CME

ACG Clinical Guideline: Diagnosis and Management of Biliary Strictures

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A biliary stricture is an abnormal narrowing in the ductal drainage system of the liver that can result in clinically and physiologically relevant obstruction to the flow of bile. The most common and ominous etiology is malignancy, underscoring the importance of a high index of suspicion in the evaluation of this condition. The goals of care in patients with a biliary stricture are confirming or excluding malignancy (diagnosis) and reestablishing flow of bile to the duodenum (drainage); the approach to diagnosis and drainage varies according to anatomic location (extrahepatic vs perihilar). For extrahepatic strictures, endoscopic ultrasound-guided tissue acquisition is highly accurate and has become the diagnostic mainstay. In contrast, the diagnosis of perihilar strictures remains a challenge. Similarly, the drainage of extrahepatic strictures tends to be more straightforward and safer and less controversial than that of perihilar strictures. Recent evidence has provided some clarity in multiple important areas pertaining to biliary strictures, whereas several remaining controversies require additional research. The goal of this guideline is to provide practicing clinicians with the most evidence-based guidance on the approach to patients with extrahepatic and perihilar strictures, focusing on diagnosis and drainage.

KEYWORDS: biliary strictures; obstructive jaundice; extrahepatic strictures; perihiliar strictures; endoscopic ultrasound; guideline

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INTRODUCTION

A biliary stricture is an abnormal narrowing in the ductal drainage system of the liver. These often result in clinically and physiologically relevant obstruction to the flow of bile but may not cause symptoms or abnormal liver tests early in their course. There are many etiologies of biliary stricture, the most common and ominous of which is malignancy, either primary or metastatic. The 2 principal management priorities in the patient with a biliary stricture are diagnosis and drainage—specifically, the confirmation or exclusion of malignancy and the restoration of flow of bile into the duodenum. Because of concrete implications in the approach to diagnosis and drainage, biliary strictures are generally divided according to their anatomic location (extrahepatic, perihilar, or intrahepatic).

The goal of this guideline is to provide clinicians with the most evidence-based guidance on the care of patients with extrahepatic and perihilar strictures, focusing on diagnosis and drainage. Although some of the diagnostic principles that are discussed in this document may be applied to intrahepatic strictures, this entity is not specifically addressed. Moreover, the management of strictures related to primary sclerosing cholangitis (PSC) is covered in a separate American College of Gastroenterology (ACG) guideline dedicated to this condition (1). Finally, we do not address surgical or oncological care of malignant strictures, except where there are endoscopic implications.

Recognizing the potential influence of commercial and intellectual conflict of interest on the guideline development process, recommendations in this document were made by a diverse group of authors using a systematic process that involved structured literature searches by librarians and independent appraisal of the quality of evidence by dedicated methodologists, all under the oversight of the ACG Practice Parameters Committee.

METHODS

The PICO formula—a standardized and validated approach to framing important clinical questions—served as the basis for recommendations in this document. By consensus, the authors developed PICO (population, intervention, comparator, and outcomes) statements pertaining to each aspect of biliary stricture

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Table 1. Grading of Recommendations, Assessment, Development, and Evaluation

Strength of recommendation	Criteria
Strong	Strong recommendations are offered when the desirable effects of an intervention clearly outweigh the undesirable effects.
Conditional	Conditional recommendations are offered when trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced.
Quality of evidence	**Criteria**
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Factors influencing the strength of the recommendation include the quality of the evidence, clinical and patient-reported outcomes, risk of harm, and costs.

evaluation and treatment. These PICO statements informed the development of corresponding recommendations. For each statement, a team of health science librarians with expertise in systematic review and clinical practice guideline development designed search strategies in PubMed (US National Library of Medicine, National Institutes of Health) and, selectively, Web of Science (Clarivate Analytics) and Cochrane Library (Wiley; EBSCO; Ovid). The databases were searched from inception through various dates in 2020–21. The search strategies used a combination of subject headings (e.g., MeSH in PubMed) and keywords for each concept. English language restrictions were applied. Search strategies were validated by ensuring the retrieval of clearly eligible studies provided by the guideline authors. To identify additional articles, the authors reviewed PubMed's similar articles and manually searched reference lists of relevant articles. At least 2 authors independently reviewed all potentially relevant articles resulting from the literature search for each PICO statement and selected eligible articles for consideration and formal appraisal.

On the basis of eligible articles, the quality of evidence for and strength of each recommendation was appraised by dedicated methodologists according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. In GRADE, the quality of evidence is divided across a spectrum from very low to high depending on the level of confidence that the true effect is close to the estimated (reported) effect and how likely further research is to change this level of confidence (Table 1). A strong recommendation (denoted in this document by the verbiage we recommend) is made when the benefits of the test or intervention in question clearly outweigh its potential disadvantages, whereas a conditional recommendation (denoted by we suggest) is made when some uncertainty remains about the balance of benefits and harms. Important clinical questions that are not amenable to the PICO structure or for which inadequate evidence exists to inform recommendations are addressed as key concepts. The key concepts are largely based on indirect evidence and expert opinion. Recommendations with associated quality of evidence and strength levels are listed in Table 2. Key concepts are listed in Table 3.

EPIDEMIOLOGY AND ETIOLOGY

The burden of biliary strictures is difficult to estimate because of lack of a specific administrative code. The estimated cost of caring for biliary disease in general is $16.9 billion annually in the United States, although this figure includes costs associated with gallbladder disease, choledocholithiasis, and other (nonobstructive) biliary disorders (2). However, of the approximately 57,000 new cases of pancreatic cancer each year in the United States, we estimate that at least 60% will cause obstructive jaundice, resulting in a minimum of 34,000 annual cases of malignant extrahepatic biliary stricture (3,4). In addition, approximately 3,000 cases of malignant perihilar stricture are expected in the United States each year (3). Patients also seek medical attention for benign strictures due to conditions such as chronic pancreatitis, PSC, autoimmune disease, and postcholecystectomy injury. Although the exact incidence is not rigorously defined, every gastroenterologist will encounter biliary strictures with reasonable frequency. The possible etiologies of biliary stricture are listed in Table 4.

Key concept

1. Biliary strictures in adults are more likely to be malignant than benign except in certain well-defined scenarios.

Summary of evidence

The existing literature demonstrates a high likelihood of malignancy as the etiology of a biliary stricture referred for endoscopic evaluation. For example, in a large series of patients with obstructive jaundice due to extrahepatic stricture (approximately half of whom had an associated mass on cross-sectional imaging) referred for endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA), malignancy was diagnosed in 73% (5). Similarly, 2 systematic reviews of studies comparing the diagnostic yield of EUS- and endoscopic retrograde cholangiopancreatography (ERCP)-based sampling for suspected malignant biliary strictures (with or without a mass on imaging) demonstrated a proportion of cancer ranging from 74% to 87% (6,7). A recent systematic review of 11 studies evaluating the diagnostic accuracy of cholangioscopy-directed biopsies for indeterminate biliary strictures—those that have undergone a negative initial evaluation *via* ERCP—reported malignancy in 193 of 356 included patients (54%) (8). Among patients with a high enough suspicion of cancer to merit surgical resection, the fraction of malignant cases has been observed to be in the range of 80%–95% (9–11).

It is important to recognize that these studies are enriched with patients at higher pretest probability of malignancy because those with obviously benign etiologies (such as an anastomotic stricture after liver transplantation) would not have been included. Nevertheless, even after accounting for this selection bias, endoscopic and surgical series suggest that whenever the etiology is not readily apparent (e.g., postoperative stricture, Mirizzi syndrome, or pseudocyst compressing the bile duct), a stricture is more likely to be

Table 2. Recommendations with associated quality of evidence and strength levels

Recommendation	Quality of evidence	Strength level
1. In patients with an extrahepatic biliary stricture due to an apparent or suspected pancreatic mass, we recommend EUS with fine-needle sampling (aspiration or biopsy) over ERCP as the preferred method of evaluating for malignancy.	Moderate	Strong
2. In patients with an extrahepatic biliary stricture due to an apparent or suspected pancreatic mass, we suggest EUS with FNB or EUS with FNA plus ROSE over FNA without ROSE as the preferred method of evaluating for malignancy.	Very low	Conditional
3. In patients with suspected malignant perihilar stricture, we recommend multimodality sampling over brush cytology alone at the time of the index ERCP.	Low	Strong
4. In patients with an extrahepatic stricture due to a benign condition, we recommend fcSEMS placement over multiple plastic stents in parallel to reduce the number of procedures required for long-term treatment.	Low	Conditional
5. In patients with an extrahepatic stricture due to resectable pancreatic cancer or cholangiocarcinoma, we suggest against routine preoperative biliary drainage. In selected patients, including those with acute cholangitis, severe pruritus, very high serum bilirubin levels, and those undergoing neoadjuvant therapy or experiencing another anticipated delay to surgery, preoperative biliary drainage is warranted.	Low	Conditional
6. In patients with a malignant extrahepatic biliary stricture that is unresectable or borderline resectable, we recommend SEMS placement over plastic stent placement.	Moderate	Strong
7. In patients with a malignant extrahepatic biliary stricture that is unresectable or borderline resectable, the evidence is insufficient to recommend for or against uSEMS vs fcSEMS placement.	Insufficient	
8. In patients with a perihilar stricture due to suspected malignancy, the evidence is insufficient to recommend for or against ERCP vs PTBD.	Insufficient	
9. In patients with malignant perihilar stricture, the evidence is insufficient to recommend for or against PS vs uSEMS placement.	Insufficient	
10. In patients with a malignant perihilar stricture due to cholangiocarcinoma who are not candidates for resection or transplantation, we suggest the use of adjuvant endobiliary ablation (photodynamic therapy or radiofrequency ablation) plus plastic stent placement over plastic stent placement alone.	Low	Conditional
11. In patients with a biliary stricture, in whom ERCP is indicated but unsuccessful or impossible, we suggest EUS-guided biliary access/drainage over PTBD, based on fewer adverse events, when performed by an endoscopist with substantial experience in these interventional EUS procedures.	Very low	Conditional

ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; fcSEMS, fully covered self-expanding metallic stent; FNA, fine-needle aspiration; FNB, fine-needle biopsy; PS, plastic stent; PTBD, percutaneous transhepatic biliary drainage; ROSE, rapid on-site evaluation; SEMS, self-expanding metallic stent; uSEMS, uncovered self-expanding metallic stent.

malignant than benign, underscoring the importance of a high index of clinical suspicion in the evaluation of this condition.

DIAGNOSIS

A priority of care when evaluating a biliary stricture is safe, accurate, and expedient diagnosis. In many (but not all) cases, a definitive diagnosis of cancer will have important implications in surgical and oncological decision making and endoscopic biliary stent selection. With rare exception, the diagnosis of malignancy in a biliary stricture cannot be confirmed or excluded on the basis of noninvasive testing. Studies evaluating various imaging modalities for biliary stricture, such as computed tomography, magnetic resonance imaging, and EUS (without FNA), have reported diagnostic accuracies in the range of 60%–80% (12,13). Biomarkers, such as CA 19-9 and CEA, have proven even less accurate (14–16). Therefore, a definitive tissue diagnosis is necessary to guide oncologic and endoscopic care in the large majority of strictures that are not surgically resectable at the time of presentation. Traditionally, ERCP has been the mainstay of tissue acquisition; however, EUS-guided sampling has significantly improved our diagnostic capabilities with substantially less risk and has thus supplanted ERCP in several scenarios. Despite important advances in the last 2 decades, however, the diagnosis of biliary strictures without an associated mass remains a major challenge in clinical practice (see below).

Diagnosis: extrahepatic stricture

Recommendation

1. In patients with an extrahepatic biliary stricture due to an apparent or suspected pancreatic mass, we recommend EUS with fine-needle sampling (aspiration or biopsy; FNA/B) over ERCP as the preferred method of evaluating for malignancy (strong recommendation, moderate-quality evidence).

Summary of evidence

ERCP-based tissue sampling (*via* transpapillary brush cytology and forceps biopsies) and EUS-FNA/B are the 2 most commonly

used modalities for evaluating biliary strictures. Data comparing the performance characteristics of ERCP-based tissue sampling and EUS-FNA/B reflect substantial heterogeneity in study design, patient populations, stricture characteristics, and the ongoing evolution of endoscopic technology. However, even earlier data that predate recent advances in fine-needle acquisition technology suggested the superiority of EUS-FNA over ERCP-based tissue sampling. For example, a prospective study published in 2004 consisting of 50 consecutive patients with obstructive jaundice (28 ultimately confirmed to have malignancy; 16 pancreatic and 12 biliary) demonstrated that the sensitivity of EUS-guided sampling (60%) was superior to that of ERCP (38%) when a pancreatic mass was present (17). More recent studies suggest an even more substantial advantage in favor of EUS-based sampling. A 2014 prospective study including 51 patients with suspected malignant biliary obstruction who underwent same-session EUS and ERCP demonstrated far superior sensitivity associated with EUS-FNA (100%) compared with ERCP-based tissue sampling (38%) for pancreatic masses (18). A more recent prospective study also demonstrated an accuracy of 100% for EUS—compared with ~55% for ERCP-based sampling of strictures with an associated mass (19).

A systematic review and meta-analysis of 8 studies published in 2018 comprising ~300 patients with suspected malignant biliary stricture demonstrated a higher pooled sensitivity of EUS-FNA (75%) vs ERCP (49%), although several studies included patients with perihilar strictures, for which the advantage of EUS-FNA is attenuated (6). Another meta-analysis comprising 6 studies of approximately 500 patients who underwent same-session EUS-FNA and ERCP affirmed that EUS-FNA was associated with a higher sensitivity than ERCP, which was driven primarily by the difference among patients with a pancreatic mass: 75% vs 47% (7).

On this basis, and recognizing that recent advances in fine-needle acquisition technology have further improved the diagnostic capabilities of EUS (see below), we recommend EUS-FNA/B over ERCP-based sampling alone for the diagnosis of biliary stricture with a known or suspected pancreatic mass. Among patients undergoing combined EUS and ERCP (for concurrent decompression), brush cytology is indicated when FNA/B is nondiagnostic or when real-time cytological evaluation is not available as the combination of both approaches appears to have the greatest diagnostic yield (7). The diagnostic approach to extrahepatic biliary strictures without an associated mass should mirror the approach to suspected malignant perihilar stricture (see Recommendation 3).

Key concept

2. In asymptomatic or minimally symptomatic patients with an extrahepatic biliary stricture due to an apparent or suspected pancreatic mass, we suggest single-session EUS and ERCP over ERCP alone for concurrent diagnosis and drainage.

Summary of evidence

Patients with a pancreatic mass resulting in an extrahepatic biliary stricture often present with painless jaundice and are usually minimally symptomatic, complaining primarily of anorexia, dyspepsia, malaise, and/or weight loss rather than severe pain, intractable nausea, and vomiting, or symptoms of acute cholangitis. Such patients occasionally undergo ERCP with biliary brush cytology and plastic stent (PS) placement at centers in which EUS is not available. Because the diagnostic yield of brush cytology is very low (20,21), and most patients with a pancreatic mass do not undergo resection without a tissue diagnosis (4,22), patients will frequently require a subsequent EUS-FNA/B for definitive diagnosis and—if malignancy is confirmed—a repeat ERCP to exchange the PS for a metallic prosthesis that is more suitable for neoadjuvant therapy (23,24). This pathway of care mandates a second procedure, resulting in an increased risk of adverse events, costs, and patient hardship. Therefore, patients who do not have a pressing need for biliary decompression are better served by referral or transfer to a center that can perform EUS-FNA/B and ERCP during the same anesthesia session. Because acute cholangitis due to malignant biliary obstruction without prior instrumentation is uncommon (25), the delay in diagnosis and drainage in minimally symptomatic patients is offset by the avoidance of a mandatory second procedure (for EUS-FNA/B, stent exchange, or both). In patients with acute cholangitis or significant symptoms, expedient ERCP is justified.

Recommendation

2. In patients with an extrahepatic biliary stricture due to an apparent or suspected pancreatic mass, we suggest EUS with FNB or EUS with FNA plus rapid on-site evaluation (ROSE) over FNA without ROSE for tissue acquisition (conditional recommendation, very-low-quality evidence).

Summary of evidence

EUS-guided FNA has been the traditional standard for evaluating masses and lymph nodes that cause biliary obstruction. FNA enables acquisition of cells *via* insertion of a hollow needle into the target tissue. Negative pressure, generated by suction, withdrawal of the stylet, and/or back-and-forth needle motion, draws cells into the needle for subsequent cytological evaluation. A meta-analysis published in 2016 comprising 20 studies (957 patients) demonstrated that EUS-FNA for the diagnosis of malignant biliary strictures (including those in the absence of a mass) had a pooled sensitivity and specificity of 80% and 97%, respectively (26).

In contrast, FNB—performed using needles with non-traditional bevel designs—was introduced to enable acquisition of larger tissue samples for improved cytological assessment and, in certain scenarios, core biopsies with preserved architecture for proper histological evaluation. Early-generation core needles, however, were technically challenging to use and were not superior to FNA in terms of tissue acquisition (27–29). In contrast, newer-generation core needles with varying bevel geometries enable tissue sampling with similar technical ease to FNA needles but higher diagnostic yield.

The reverse bevel needle was the first of these newer-generation needles to become commercially available and is thus the most widely studied. Although there is significant heterogeneity in study design and outcomes within the literature comparing reverse bevel FNB to standard FNA, studies generally demonstrate that, at the very least, reverse bevel FNB reduces the number of passes necessary for diagnosis and does appear to improve diagnostic performance (30–32). Indeed, 3 of 4 meta-analyses of randomized controlled trials (RCTs) published since 2018 (that include mainly reverse bevel studies) demonstrated superior diagnostic accuracy associated with reverse bevel FNB without an increase in adverse events (33–36).

More recently introduced FNB needles also appear advantageous in comparison to standard FNA. A randomized crossover study comparing the fork-tip needle geometry (2 sharp leading tips

Table 3. Key concepts

1. Biliary strictures in adults are more likely to be malignant than benign except in certain well-defined scenarios.
2. In asymptomatic or minimally symptomatic patients with an extrahepatic biliary stricture due to an apparent or suspected pancreatic mass, we favor single-session EUS and ERCP for concurrent diagnosis and drainage over ERCP alone.
3. In patients with a suspected malignant perihilar stricture due to cholangiocarcinoma, EUS-FNA/B and percutaneous biopsy of the primary lesion (perihilar stricture or mass) should be avoided. Instead, intraductal sampling should be favored. EUS-FNA/B (or percutaneous biopsy) should only be performed to sample associated adenopathy.
4. If the etiology of a biliary stricture remains uncertain despite ERCP with multimodality intraductal sampling, additional diagnostic options exist and can be selectively deployed according to clinical context, stricture characteristics, and resource availability.
5. An extrahepatic biliary stricture due to a benign condition should be treated for 12 months when using multiple plastic stents and for at least 6 months when using fcSEMSs, although some evidence suggests that 12 months of fcSEMS therapy is advantageous. When aiming for 12-month fcSEMS dwell time, stent exchange at the 6-month mark should be considered to reduce the risk of embedment.
6. In patients with a benign biliary stricture and gallbladder *in situ*, endoscopists should consider treatment with multiple plastic stents instead of fcSEMSs if the cystic duct orifice cannot be avoided by the metallic prosthesis because of a possible increased risk of acute cholecystitis.
7. A diagnosis of malignancy should be confirmed before placement of a uSEMS across a biliary stricture.
8. In patients with malignant extrahepatic biliary stricture who are potential candidates for pancreaticoduodenectomy and undergo uSEMS placement, we suggest placing the proximal (upstream) end of the prosthesis at least 1.5 cm below the biliary confluence.
9. In patients with obstructive jaundice due to a malignant perihilar stricture who are otherwise asymptomatic and have declined or are not candidates for additional treatment, palliative drainage is not mandatory and should be decided on an individual case basis.
10. When ERCP is pursued to diagnose and treat perihilar strictures, it should be performed by endoscopists with sufficient training and/or experience in advanced biliary endoscopy. High-quality ERCP in patients with a perihilar stricture includes preprocedure review of available cross-sectional imaging, careful intraprocedural use of contrast injection and fluoroscopy, and administration of antibiotics when there is concern for slow or incomplete drainage of contrast from opacified bile ducts.
11. In patients with a perihilar stricture, hepatobiliary drainage should be pursued in a volumetric sectorial fashion and not in terms of unilateral vs bilateral drainage. The technical goal is to drain >50% of the nonatrophic liver, with each sector contributing roughly one-third of the liver's volume.
12. If SEMS is chosen for drainage of a malignant perihilar stricture, an effective drainage strategy using plastic stent(s) should be proven first.

ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; fcSEMS, fully covered self-expanding metallic stent; FNA, fine-needle aspiration; FNB, fine-needle biopsy; SEMS, self-expanding metallic stent; uSEMS, uncovered self-expanding metallic stent.

on opposite sides of the needle lumen) to standard FNA in 108 patients referred for EUS-guided sampling of solid pancreatic masses demonstrated that FNB had greater sensitivity (82% vs 71%) and accuracy (84% vs 75%) ($P < 0.001$) and shorter sampling and pathology viewing times (37). Similarly, another randomized crossover study comparing the Franseen needle design (3 symmetric cutting edges) to standard FNA in 46 patients showed that preserved tissue architecture (93.5% vs 19.6%, $P < 0.0001$) and cell block diagnostic yield (97.8% vs 82.6%, $P = 0.03$) were significantly higher after FNB (38). There was no difference in adverse events between the 2 needle types in these studies. These findings are generally consistent with those of retrospective studies of the fork-tip and Franseen FNB needles (39). As with the reverse bevel studies, this literature is also difficult to interpret with a high level of confidence because of substantial heterogeneity in study design and outcome assessment.

Rapid on-site evaluation of EUS-acquired FNA specimens has been shown to improve diagnostic performance but is costly and not universally available (40). A potential advantage of EUS-FNB is that it appears to obviate the need for ROSE. A multicenter study recently demonstrated that EUS-FNB alone is noninferior to FNA + ROSE at comparable cost but required fewer needle passes (41). Similarly, a meta-regression analysis specifically focusing on the impact of ROSE demonstrated no difference between FNB and FNA + ROSE but superiority of FNB in the absence of onsite evaluation (42). Another recent retrospective study demonstrated that EUS-FNA + ROSE was similar to EUS-FNB alone but suggested that FNB + ROSE could offer incremental diagnostic yield in challenging cases (43). There are no published randomized trials comparing FNA + ROSE vs FNB + ROSE.

Genomic profiling-guided precision therapy is emerging and will play a growing role in the treatment of patients with pancreaticobiliary malignancies. Two RCTs and a retrospective study have demonstrated that FNB results in higher DNA concentrations (fork tip, 50 patients) (44), nucleic acid yield (Franseen, 36 patients) (45), and sufficient specimens for microsatellite instability testing (Franseen, 99 patients) (46) compared with FNA of pancreatic lesions.

In summary, despite limitations in the data, the existing literature in aggregate supports the use of FNB or FNA + ROSE over FNA alone. Additional research is necessary to clarify whether FNB remains advantageous relative to FNA where ROSE is available. FNB will likely continue to play a growing role in genomic profiling and other advanced diagnostics.

Diagnosis: perihilar stricture

Key concept

3. In patients with a suspected malignant perihilar stricture due to cholangiocarcinoma, EUS-FNA/B and percutaneous biopsy of the primary lesion (perihilar stricture or mass) should be avoided. Instead, intraductal sampling should be favored. EUS-FNA/B (or percutaneous biopsy) should only be performed to sample associated lymphadenopathy.

Summary of evidence

Cholangiocarcinoma is notoriously difficult to diagnose *via* intraductal sampling (47,48). EUS-FNA/B or percutaneous biopsy (when a hilar mass or bile duct thickening is present) has a higher diagnostic accuracy compared with ERCP-guided

sampling (49), although their use is controversial because of the associated risk of transperitoneal needle tracking and consequent peritoneal seeding. In a widely cited study from the Mayo Clinic, peritoneal metastasis occurred in 5 of 6 patients (83%) who had a positive transperitoneal biopsy (endoscopic or percutaneous) for cholangiocarcinoma during liver transplant evaluation, much higher than the rate observed in those who underwent intraductal sampling or no biopsy at all (50). The true impact of this phenomenon remains unclear as another large study demonstrated that EUS-FNA did not affect overall or progression-free survival in a cohort of patients with cholangiocarcinoma, almost 80% of whom underwent curative-intent surgery (51). Nevertheless, on the basis of concern over peritoneal seeding, most transplantation protocols for cholangiocarcinoma consider prior transperitoneal sampling an absolute exclusion criterion. Because transplantation represents the only potentially curative option in many patients with perihilar cholangiocarcinoma (52), EUS-FNA/B (and percutaneous biopsy) of the primary lesion is discouraged in favor of intraductal sampling methods that do not appear to increase the risk of peritoneal seeding. EUS does play an important role in the diagnosis and staging of malignant perihilar strictures by assessing regional adenopathy, which can be biopsied without risk of transplant exclusion because a positive lymph node is in itself a contraindication to liver transplantation. EUS-FNA/B of visualized lymph nodes regardless of their appearance is advisable, as malignant involvement cannot be reliably predicted by endosonographic morphology and echofeatures alone (53).

Table 4. Etiology of biliary strictures

Malignant, primary
• Pancreatic cancer
• Cholangiocarcinoma
• Gallbladder cancer
• Hepatocellular carcinoma
• Ampullary cancer
• Lymphoma
• Rare: cystadenocarcinomas, mixed hepatocellular-cholangiocellular cancer
Malignant, metastatic
• Colon cancer
• Breast cancer
• Renal cell cancer
• Rare: squamous cell carcinoma
Fibroinflammatory
• Chronic pancreatitis
• Primary sclerosing cholangitis
• Autoimmune (immunoglobulin G [IgG] 4–mediated) pancreatitis
• IgG4-mediated cholangitis
• Sarcoidosis
• Recurrent pyogenic cholangitis
• Extrinsic compression by a pancreatic fluid collection
Iatrogenic
• Cholecystectomy
• Liver transplantation
• Local cancer treatment (chemoembolization, radiation therapy, microwave ablation, and radiofrequency ablation)
Vascular
• Portal hypertensive biliopathy
• Ischemic biliary injury
AIDS cholangiopathy
Mirizzi syndrome

Recommendation

3. In patients with suspected malignant perihilar stricture, we recommend multimodality sampling over brush cytology alone at the time of the index ERCP (strong recommendation, low-quality evidence).

Summary of evidence

As above, the diagnosis of malignant perihilar strictures is particularly challenging due to the often desmoplastic nature of cholangiocarcinoma, which also has a tendency for subepithelial spread. The primary diagnostic challenge in this disease process is falsely negative results (low sensitivity) as falsely positive samples (low specificity) are uncommon. Brush cytology has been the traditional cornerstone of the initial sampling of biliary strictures because of its relative technical ease and widespread availability (including the requirement for standard cytopathological handling and interpretation). However, a meta-analysis published in 2013 comprising 1,556 patients (including 33% with pancreatic cancer and 36% with cholangiocarcinoma) demonstrated a composite sensitivity of brush cytology of only 41.6% (21). Subsequent studies have demonstrated sensitivity rates clustering around 50%–60% (54,55), although notable outliers have reported sensitivities as low as 6% (20) or in the range of 75% (56); however, one of these studies used ROSE of brush cytology specimens (57). Nevertheless, the performance characteristics of this diagnostic modality are inadequate to drive clinical decision making, and thus, additional sampling techniques are now commonly performed.

Pediatric, standard, and large-capacity biopsy forceps fit through the accessory channel of a duodenoscope and across the elevator and may be advanced to the level of a stricture under fluoroscopic guidance for tissue sampling. Studies have shown that the sensitivity of ERCP-directed forceps biopsies ranges from 40% to 88% (58–61). In aggregate, the existing literature suggests that the pooled yield of forceps biopsy is not substantially higher than brush cytology; however, the combination of both is likely diagnostically superior (62–65). Indeed, a meta-analysis (9 studies) published in 2015 that includes 730 patients with indeterminate biliary strictures showed a pooled sensitivity of 45% and 48% for brushings and biopsies, respectively, but a sensitivity of 59% for the combination of both modalities (66).

Cholangioscopy permits direct visualization of biliary strictures and targeted biopsies of concerning (and potentially higher-yield) areas. The reported sensitivity of visual stricture assessment for diagnosing malignancy ranges from 64% to 95% (67–69), although the practical value of cholangioscopy remains tissue acquisition because endoscopic impression is not an accepted standard on which oncological (and other) decisions are made. Two recent meta-analyses assessing the yield of cholangioscopy-directed biopsies in patients with negative prior sampling demonstrated an overall sensitivity of 60%–75% and sensitivity for detecting cholangiocarcinoma of 66.2% (8,70). A comparative study indicated that cholangioscopy-directed biopsies had a greater sensitivity than brush cytology and forceps biopsies (20).

Finally, fluorescence *in situ* hybridization (FISH) has gained traction as a component of multimodality sampling for biliary strictures. FISH uses fluorescently labeled DNA probes to assess

cells for chromosomal abnormalities, which are associated with malignancy. A study of approximately 500 consecutive patients undergoing ERCP with brush cytology for evaluation of pancreaticobiliary strictures found that the addition of FISH increases the sensitivity from 20.1% with cytology alone to 42.9% (71). In this study, the presence of polysomy on FISH was associated with an odds ratio of >77 for carcinoma. Multiple additional studies and a meta-analysis have demonstrated that FISH adds substantial diagnostic value to brush cytology alone (65,72–74). Important considerations are that (i) the favorable performance characteristics of FISH are attenuated in the presence of PSC (presumably because of the substantial inflammatory component) (75,76) and (ii) although some surgeons may use FISH results as a contributing factor in the decision to perform a resection, it is highly uncommon for oncologists to offer chemotherapy on the basis of an abnormal FISH analysis alone.

In summary, fluoroscopy-directed biopsies, cholangioscopy-directed biopsies, and FISH each appear to add diagnostic value to brush cytology alone. Therefore, we recommend that at least 2 diagnostic sampling modalities are used at the time of ERCP-based biliary stricture evaluation. In addition, there is a rationale to use 3–4 of the aforementioned modalities at the time of the initial evaluation if they can be performed safely, and trimodality sampling is supported by retrospective data (77,78). Within the GRADE framework, the safety of adding another sampling modality during ERCP and the low yield of brush cytology justified a strong recommendation despite low-quality evidence. Additional research will clarify the optimal sampling strategy during the index and subsequent ERCPs. As discussed above, the principles that inform this recommendation also apply to extrahepatic biliary strictures without an associated mass.

Diagnosis: additional considerations for the indeterminate biliary stricture

Key concept

4. If the etiology of a biliary stricture remains uncertain despite ERCP with multimodality intraductal sampling, additional diagnostic options exist and can be selectively deployed according to clinical context, stricture characteristics, and resource availability.

Summary of evidence

An indeterminate biliary stricture is defined as one for which a diagnosis has not been established despite initial ERCP with intraductal sampling. A number of additional diagnostic modalities may enhance the ability to differentiate benign from malignant strictures and may serve as an adjunct to repeat intraductal sampling in patients with an indeterminate stricture.

Although primarily used for the diagnosis of extrahepatic strictures with an associated mass (see above), EUS-FNA/B may also play an important role in the evaluation of indeterminate perihilar strictures (49). As expressed in Key concept 3, EUS-FNA/B of the primary lesion (perihilar duct wall thickening, intraductal or periductal mass) should be avoided because of the increased risk of peritoneal tumor seeding and consequent impact on liver transplant candidacy. However, EUS-based sampling of the primary lesion may provide a definitive diagnosis in patients who are not candidates for liver transplantation. In addition, as above, EUS-guided sampling of portal adenopathy can be performed without risk of transplant exclusion because a positive lymph node is in itself a contraindication. Finally, indeterminate strictures in the extrahepatic bile duct are not treated with transplantation and can thus be sampled directly, akin to pancreatic head masses because the needle track is typically contained within the field of surgical resection.

Probe-based confocal laser endomicroscopy (pCLE)—which is introduced into the bile duct during ERCP to obtain an real-time optical biopsy of the target tissue—can help distinguish inflammatory from malignant strictures on the basis of 2 validated classifications systems (79,80). In a prospective multicenter study, the combination of cholangiographic impression, pCLE interpretation, and histopathology was reported to have a sensitivity and accuracy in the range of 90% (81). However, similar to the limitation of visual analysis of strictures using cholangioscopy, the performance characteristics of pCLE interpretation do not meet the threshold necessary to drive oncological decision making at the large majority of institutions. Following the precedent of hepatocellular carcinoma—a malignancy that can be diagnosed definitively on the basis of imaging alone (i.e., without histopathological confirmation)—pCLE-based optical biopsy, especially with additional development that includes molecular markers and artificial intelligence, may ultimately obviate the need for histopathology in the evaluation of biliary strictures, but it currently remains an adjunct diagnostic modality at select referral centers. Similarly, intraductal ultrasound—in which a high-frequency ultrasound probe advanced through the ERCP scope into the biliary tree to acquire a cross-sectional view of the stricture and surrounding duct—has been reported to have an accuracy of up to 92% (82,83); however, the inability to acquire tissue and its declining availability limit its impact in clinical practice.

Enhanced testing of intraductal tissue samples may improve the sensitivity of diagnosing malignancy in indeterminate strictures. In a prospective study of 252 patients, a 28-gene next-generation sequencing panel improved the sensitivity of pathological evaluation for malignancy from 35% to 77% for biliary brushings and from 52% to 83% for biliary biopsies (84). Like FISH, next-generation sequencing may prove to be an important adjunct to standard histologic evaluation, although the technology is still in evolution and not widely available.

Several additional methods of assessing biliary strictures, such as intraductal narrow-band imaging, optical coherence tomography, digital image analysis, bile analysis, and circulating tumor DNA (liquid biopsy), remain in evolution, do not play a concrete role in clinical practice, and are beyond the scope of this guideline.

It is important to consider that when definitive diagnosis of an indeterminate stricture proves difficult, discussion at a multidisciplinary tumor board for additional pathologic, radiographic, surgical, and oncological input is advisable. Tumor board review and/or surgical consultation may be requested at any time in the patient's care pathway, but especially after 2 negative sampling sessions if the concern for undiagnosed malignancy remains.

DRAINAGE

Restoration of the physiologic flow of bile into the duodenum is a principal objective in the management of patients with biliary stricture. There is substantial variability in the difficulty and risk of achieving adequate drainage depending on the location and complexity of the stricture. Generally speaking, compared with extrahepatic strictures, the drainage of perihilar strictures is more technically challenging and riskier. The complexity of such strictures is stratified according to the Bismuth-Corlette

classification system, wherein type 1 strictures are isolated to the common hepatic duct (and are thus most easily drained); type 2 strictures involve the biliary confluence but not the intrahepatic ducts; type 3 strictures involve the confluence and either the right intrahepatic system (3a) or the left intrahepatic system (3b); and type 4 strictures involve the confluence and both the right and left systems (and are thus the most challenging to drain).

The goals of drainage should be to alleviate symptoms (when present), to reduce serum bilirubin to a level at which chemotherapy can be safely administered (typically ~2.5–3.5 mg/dL) (85,86), and to optimize surgical outcomes in certain scenarios outlined below. In addition, a large database study of approximately 14,000 patients with obstructive jaundice due to pancreatic cancer demonstrated that biliary drainage reduces mortality by approximately 50% (87). Limited retrospective data in patients with malignant hilar obstruction show the same thing, although these studies were not large or rigorous enough to adequately address confounding (e.g., less advanced or aggressive malignancy has lower mortality rates and results in strictures that are easier to drain) (88–90). Even in the absence of concrete symptoms, and independent of mortality, it appears possible that adequate biliary drainage may provide quality of life benefits, such as improved appetite, energy, and sleep (see Key concept 9 below) (91). In this section, we provide recommendations and address key concepts that aim to improve clinical success and reduce adverse events related to nonsurgical drainage of biliary strictures.

Drainage: extrahepatic stricture, benign

Recommendation

4. In patients with an extrahepatic stricture due to a benign condition, we recommend fully covered self-expanding metallic stent (fcSEMS) placement over multiple plastic stents (MPSs) in parallel to reduce the number of procedures required for long-term treatment (conditional recommendation, low-quality evidence).

Summary of evidence

ERCP is the preferred modality for durable treatment of extrahepatic biliary strictures of benign etiology. Placement of a single PS results in inadequate long-term resolution for most stricture types and is thus not recommended (92,93). However, sequential placement of MPSs in parallel to remodel the stricture has been established for some time as an effective treatment option (94,95). Typically, multiple ERCPs to exchange and increase the number of stents over an extended period of time (Rome protocol) are required to minimize long-term recurrence. Using this approach, ERCP is generally repeated every 3 months to exchange stents and upsize to the maximum number of 10-French stents that can be placed across the stricture for a median of 12 months of continuous therapy. Observational data and a meta-analysis demonstrate that MPSs are associated with a composite long-term stricture resolution rate of approximately 80% (96), although some retrospective studies have suggested resolution rates in excess of 90% (97).

In the last decade, there has been increasing interest in use of fcSEMSs to treat benign biliary strictures (98). fcSEMSs are easier and faster to place and exchange than MPSs, exert greater radial force after the initial ERCP, and do not require programmatic exchange through the duration of intended dwell time, reflecting important potential advantages over the traditional MPS treatment paradigm. It is important to consider, however, that only 1 commercially available fcSEMS is approved in the United States for the treatment of benign biliary strictures related to chronic pancreatitis, and therefore, the use of any fcSEMS for the management of other forms of benign stricture is considered off-label.

To date, 7 RCTs comparing fcSEMSs and MPSs have been published. A methodologically rigorous US-based trial that included 112 patients with benign biliary strictures of various etiologies found that the fcSEMS was noninferior to the MPS in terms of stricture resolution (92.6% vs 85.4%) but was associated with faster time (181 vs 225 days) and fewer ERCPs (2.14 vs 3.24, $P < 0.001$) to resolution (99). In this trial, there was no difference in recurrence and adverse event rates. It is important to consider that patients with a stricture in close proximity to the hilum, those with an intact gallbladder in whom the cystic duct would be jailed off by the fcSEMS, and those with a bile duct diameter <6 mm were excluded from this study. Two meta-analyses and a subsequent international multicenter RCT in patients with chronic pancreatitis-related strictures have affirmed these findings—that there is no difference between the 2 strategies in terms of stricture resolution (80%–90%), recurrence (15%–20%), or serious adverse events (15%–20%), but the fcSEMS strategy requires fewer ERCPs to achieve clinical success (100–102).

This conclusion appears consistent across varying etiologies of benign biliary stricture. For example, in the 2 randomized trials focused exclusively on chronic pancreatitis-related strictures, there was no difference in clinical success between treatment arms with similar rates of stent migration and other complications, whether treatment was continued for 6 or 12 months (102,103). Both trials showed a statistically significant reduction in the number of ERCP sessions in patients assigned to receive fcSEMSs. RCTs in patients with anastomotic strictures related to liver transplantation have shown similar overall findings (104–106). It is important to note, however, that one of these studies, which enrolled 64 patients, demonstrated a significantly higher recurrence rate after treatment with fcSEMSs, potentially explained by the longer duration of treatment in the MPS group (1 year) compared with fcSEMSs (6 months) (106). This same study demonstrated more complications associated with fcSEMSs, largely attributable to post-ERCP pancreatitis, which was hypothesized to be due to the lack of biliary sphincterotomy before self-expanding metallic stent (SEMS) placement (106). This complication has been observed in other studies of fcSEMSs, and thus, biliary sphincterotomy in this context may be advisable (107).

There have been no RCTs addressing this question specifically in patients with postcholecystectomy strictures, for which PSs may be preferable given their proximity to the hepatic hilum and the potential for fcSEMSs to occlude an intrahepatic ductal system. However, observational data in this patient population also show comparable outcomes with fcSEMSs and MPSs (108,109).

Overall, existing evidence supports the use of fcSEMSs over MPSs for benign biliary strictures on the basis of comparable treatment success and safety but the need for fewer ERCPs, with associated advantages in terms of patient convenience, health care resource utilization, and costs (104,106). MPSs continue to play an important role for the treatment of benign strictures in several scenarios: (i) when the stricture is close to the hepatic hilum (within 1–1.5 cm); (ii) when the gallbladder is present, but the cystic duct orifice cannot be avoided by the fcSEMS (see Key concept 6); (iii) when fcSEMSs have previously migrated or are not well tolerated (because their radial force can result in significant pain after the

initial placement that does not subsequently improve in some patients); and (iv) when recurrence after fcSEMS removal has occurred (vs repeat fcSEMS with longer dwell or surgical referral).

Key concept

5. An extrahepatic biliary stricture due to a benign condition should be treated for 12 months when using MPSs and for at least 6 months when using fcSEMSs, although some evidence suggests that 12 months of fcSEMS therapy is advantageous. When aiming for 12-month fcSEMS dwell time, stent exchange at the 6-month mark should be considered to reduce the risk of embedment.

Summary of evidence

The end point of stent therapy for benign biliary stricture remains unclear. Cholangiographic resolution of the stricture—defined as a residual diameter of the stricture no less than 75% the size of duct above and below—has been shown to be an independent predictor of long-term response and was used as the primary outcome measure in a large methodologically rigorous RCT evaluating stent therapy for benign strictures (99,110). Other investigators have proposed complete disappearance of the stricture and/or the ability to maneuver an extraction balloon across the region of the stricture with minimal to no resistance (especially in the upstream direction) as an indicator of treatment success (94,111). However, because radiographic resolution of a stricture (especially with fcSEMS) may occur within a matter of days—a duration of stent therapy that would not be expected to result in long-term response—treatment for a fixed period of time, in addition to the absence of a mechanically relevant stenosis at the time of stent removal, has emerged as the preferred end point.

The optimal duration of stent therapy to durably remodel a stricture, however, remains uncertain. In most studies, treatment time has ranged from 3 to 12 months. In the seminal article describing the strategy of increasing the number of MPSs with each sequential ERCP until resolution (Rome protocol), patients were treated for a mean of 12.1 $\pm$ 5.3 months with a long-term response rate of 89% at 4 years (94). Most studies affirming the efficacy of MPSs used a treatment duration of around 1 year (112–114). Among patients treated with fcSEMSs, longer duration of treatment (6 months or more) also appears to be advantageous. In 1 retrospective multicenter study of 134 patients who experienced a stricture resolution rate of 78%, regression analysis found that treatment duration $\geq$120 days was associated with long-term success (115). In another retrospective study of 123 patients from 5 tertiary centers in the United States, longer dwell time (6 months vs 3 months) was found to be the only variable independently associated with clinical success (116). A third multicenter observational study comprising 133 patients demonstrated higher stricture resolution when dwell time exceeded 3 months (117). A meta-analysis found that 6 months of treatment was associated with better outcomes than 3 months, confirming the inverse association between duration of stent therapy and recurrence (100).

Some evidence suggests that 12 months of fcSEMS therapy may be even more advantageous. In a prospective study of patients with benign biliary strictures, a 10–12-month fcSEMS dwell time was associated with resolution in 79.7% of patients with chronic pancreatitis—traditionally believed to be more resistant to stent therapy (117,118)—compared with a 68.3% resolution rate in patients with liver transplant-related strictures who were stented for a median of only 5 months (98). An aforementioned RCT of MPSs vs fcSEMSs demonstrated a significantly lower recurrence rate among patients who were treated with MPSs for 1 year compared with fcSEMSs for 6 months (106). In addition, a rigorously conducted multicenter RCT comparing MPSs with fcSEMSs for chronic pancreatitis confirmed an overall clinical success rate of 75.8% at 2 years after 12 months of therapy (102).

Although 1 commercially available fcSEMS has received US Food and Drug Administration (FDA) clearance for a dwell time of up to 12 months for chronic pancreatitis strictures, the principal concerns of a prolonged dwell time for this prosthesis type are stent migration and embedment, the latter of which may significantly complicate subsequent removal. However, the rate of migration appears to be equivalent between MPSs and fcSEMSs (see Recommendation 4) and, based on the meta-analysis of 37 studies (1,677 patients), occurs in approximately 10% of cases (119,120). Migration has been associated with a substantially reduced likelihood of stricture resolution (98,117). As discussed above, pivoting to MPS after premature fcSEMS migration may be required. It should be noted that a commercially available fcSEMS with anchoring flanges may result in fewer instances of migration. This device does not have FDA 510(k) premarketing clearance for removability in the United States but does possess European CE Mark and Health Canada approval for removal of the device up to 12 months after implantation for the treatment of benign or malignant biliary strictures.

The inability to remove an fcSEMS due to tissue hyperplasia or proximal migration remains an important concern with serious potential implications, especially in patients who are suboptimal surgical candidates. In the aforementioned prospective study of patients who underwent an fcSEMS dwell time of 10–12 months, 85% of stents were removed using standard maneuvers, and only 3 required the stent-in-stent technique to treat hyperplastic tissue anchoring the stent in place (98). However, in the randomized trial of MPSs vs fcSEMSs for chronic pancreatitis strictures (12-month dwell time), 20% of patients in the fcSEMS group required a second procedure for stent removal, and 7 (of 90) required the stent-in-stent technique (102). In contrast, all 57 patients in a randomized trial in which the mean fcSEMS treatment duration was 6 months had a successful stent removal during the first attempt (99). Thus, it appears that fcSEMS dwell time in excess of 6 months increases the risk of tissue overgrowth and stent embedment, and on this basis, some experts exchange the fcSEMS after 6 months of dwell time if the goal is to continue therapy for a full year.

In summary, based on available evidence, benign biliary strictures should be treated with MPSs for 12 months and for at least 6 months for fcSEMSs, although some data suggest that 12 months of therapy may provide additional long-term benefit. FcSEMS embedment, which can result in the need for additional ERCPs and advanced removal techniques, appears more common with a 12-month dwell and may justify stent exchange after 6 months.

Key concept

6. In patients with a benign biliary stricture and gallbladder *in situ*, endoscopists should consider treatment with MPSs instead of fcSEMSs if the cystic duct orifice cannot be avoided by the metallic prosthesis because of a possible increased risk of acute cholecystitis.

Summary of evidence

Placement of an fcSEMS in a patient with an intact gallbladder may lead to acute cholecystitis by jailing off the cystic duct orifice and impeding flow of bile from the gallbladder. There are limited data on the incidence of acute cholecystitis after fcSEMS placement

for benign strictures because endoscopists typically avoid this stent type when the cystic takeoff may become occluded. Indeed, as mentioned above, the largest RCT comparing fcSEMSs with MPSs for all kinds of benign strictures excluded patients in whom the cystic duct orifice would have been covered by the prosthesis (99). Meta-analyses suggest that this phenomenon occurs in only 1% of patients with benign biliary strictures after fcSEMS placement, although this rate is likely an underestimate because the denominator of patients in whom fcSEMS use was intentionally avoided due to concern for acute cholecystitis or in whom the cystic takeoff was definitely covered by the stent is unknown (100).

In a multicenter prospective cohort study of fcSEMSs for benign strictures, cholecystitis was reported in 3 of 43 (7.0%) patients with chronic pancreatitis with intact gallbladders if the cystic takeoff was covered compared with no cases among the 58 patients with chronic pancreatitis if the cystic duct orifice could be avoided (98). Similarly, in the large randomized trial of fcSEMSs vs MPSs for chronic pancreatitis strictures, cholecystitis occurred in 3 (of 69) patients in the fcSEMS group vs in 1 (of 72) patients in the MPS group (102). Neither difference was statistically significant, but these findings suggest the possibility of increased cholecystitis risk when the cystic takeoff is occluded by a covered prosthesis.

On the basis of these limited data and anecdotal experience, and because MPSs are not inferior to fcSEMSs in terms of stricture resolution and recurrence (see Recommendation 4), we believe that it is reasonable to favor MPSs in patients with gallbladder *in situ* when the cystic takeoff cannot be avoided by the fcSEMS. Alternatively, prophylactic transpapillary gallbladder stent placement can be used before fcSEMS placement with apparent success; however, this approach requires a higher level of technical expertise and is not always feasible (121,122).

Drainage: extrahepatic stricture, malignant

Recommendation

5. In patients with an extrahepatic stricture due to resectable pancreatic cancer or cholangiocarcinoma, we suggest against routine preoperative biliary drainage (conditional recommendation, low-quality evidence). In selected patients, including those with acute cholangitis, severe pruritus, very high serum bilirubin levels, and those undergoing neoadjuvant therapy or experiencing another anticipated delay to surgery, preoperative biliary drainage is warranted.

Summary of evidence

Persistent cholestasis as a result of malignant biliary obstruction has been associated with a number of complications after pancreaticoduodenectomy, including anastomotic leak and poor wound healing (123,124). Cholestasis also leads to a proinflammatory state that has been linked to coagulopathy and renal and myocardial dysfunction (125–127). On this basis, routine preoperative biliary drainage had traditionally been used to reduce surgical morbidity and mortality in patients with jaundice undergoing pancreaticoduodenectomy for an extrahepatic biliary stricture.

However, despite compelling preclinical data, early randomized trials and meta-analyses comprising these trials and observational studies did not find a clear benefit associated with preoperative biliary drainage (128,129). In 2010, a methodologically rigorous multicenter RCT comparing preoperative drainage (mostly *via* ERCP) to early pancreaticoduodectomy for patients with obstructive jaundice due to pancreatic cancer provided additional clarity in this area (130). Among 202 randomized patients, serious adverse events occurred in 39% of patients in the early surgery group compared with 74% of patients in the preoperative biliary drainage group (relative risk [RR] of complications after early surgery 0.54, 95% confidence interval [CI] 0.41–0.71). The difference in the overall complication rate was driven largely by adverse events related to preoperative drainage (e.g., early stent occlusion). Surgical adverse events were similar in the 2 groups, contradicting the concern that operating in patients with jaundice confers increased operative risk. An important limitation of this RCT was the routine use of PSs rather than SEMSs, which likely contributed to the high morbidity observed in the drainage group. In addition, it is important to recognize that patients with a bilirubin level in excess of 14.6 mg/dL were excluded, and thus, the findings may not apply to patients with jaundice of this magnitude.

In 2017, an updated meta-analysis of 3 RCTs and 22 retrospective studies found that ERCP for preoperative drainage was associated with an increased odds of complications overall (odds ratio [OR] 1.40, 95% CI 1.14–1.72) and wound infections specifically (OR 1.94, 95% CI 1.48–2.53) (131). No meaningful difference in mortality, pancreatic fistula, or intra-abdominal abscess was observed. This meta-analysis, however, did not stratify outcomes according to stent type. Nevertheless, based on the strongest available evidence, routine preoperative biliary drainage for patients with resectable pancreatic cancer or extrahepatic cholangiocarcinoma is not advised.

Certain patients, however, may warrant preoperative biliary drainage, including those with acute cholangitis or a serum bilirubin level greater than 14.6 mg/dL (because, as above, this was an exclusion criterion in the most rigorous trial on this topic). In addition, an evolving trend in clinical practice—supported by oncological guidelines—is to consider neoadjuvant therapy in any patient with resectable pancreatic cancer, especially those with high-risk features, such as a large primary tumor, a very elevated CA 19-9 level, or sizeable regional lymph nodes (132,133). Thus, many patients with obstructive jaundice due to a malignant extrahepatic stricture will require biliary decompression before initiating preoperative chemo(radio)therapy. Similarly, patients who experience other significant delays to surgery (typically defined as >2 weeks), to address competing comorbidities or improve nutritional status, for example, may benefit from drainage, although this scenario has never been specifically studied.

Recommendation

6. In patients with a malignant extrahepatic biliary stricture that is unresectable or borderline resectable, we recommend SEMS placement over PS placement (strong recommendation, moderate quality evidence).

Summary of evidence

In patients with pancreatic cancer or extrahepatic cholangiocarcinoma who are not undergoing immediate curative resection, biliary drainage is indicated to relieve symptoms and permit the safe delivery of chemotherapy. Both PSs and SEMSs are effective for initial relief of biliary obstruction. However, a robust evidence base that includes several randomized trials, large-scale observational studies, and meta-analyses demonstrates that SEMSs provide significantly longer stent patency and reduce cholangitis events, leading to far fewer interruptions in neoadjuvant or palliative chemotherapy (23,24,134–141). Accordingly, studies have found

that SEMSs result in fewer reinterventions, lower rates of hospitalization due to stent-related complications, and fewer additional days of hospitalization compared with PSs (134,140,141). SEMS placement has also been associated with better general and disease-specific quality of life compared with PSs (142). Although some randomized trials and a 2006 Cochrane review showed equivalent survival between the 2 stent types (137,139,143), recent meta-analyses have suggested a survival advantage associated with SEMSs (24,144). On this basis, SEMSs are recommended over PSs when drainage of malignant extrahepatic biliary stricture is indicated. This recommendation also applies to patients with extrahepatic biliary stricture attributable to a resectable malignancy who will undergo pre-operative neoadjuvant therapy.

Key concept

7. A diagnosis of malignancy should be confirmed before placement of an uncovered SEMS (uSEMS) across a biliary stricture.

Summary of evidence

uSEMSs generally become permanently anchored to the bile duct wall as a result of tissue ingrowth into the open mesh, even in the absence of malignancy (145). Because of this tissue hyperplasia and stone/sludge formation that is common with indwelling biliary prostheses, the median patency of uSEMSs, even in benign disease, is approximately 9 months (146). Therefore, when uSEMSs are placed across benign strictures and become permanently embedded, recurrent stent occlusion and chronic low-grade obstruction leading to secondary biliary cirrhosis or secondary sclerosing cholangitis are serious long-term considerations. Although removal using the stent-in-stent technique is possible (147,148), uSEMS retrieval is technically challenging, risky, and not always successful, and surgical bypass to achieve drainage upstream of the stent may be necessary. In suboptimal surgical candidates, lifelong periodic ERCPs may be the patient's only long-term option. Anecdotally, such patients are frequently hospitalized with stent occlusion and cholangitis despite programmatic ERCPs to ensure patency. For these reasons, a confirmed diagnosis of cancer should be established before uSEMS placement, even when the overall clinical suspicion of malignancy is high as clinical, laboratory, and radiographic findings suggestive cancer are not infallible (CA 19-9 level can be markedly elevated in the setting of jaundice, and/or cholangitis and hepatic abscesses can be mistaken for metastases).

Key concept

8. In patients with a malignant extrahepatic biliary stricture who are potential candidates for pancreaticoduodenectomy and undergo uSEMS placement, we suggest placing the proximal (upstream) end of the prosthesis at least 1.5 cm below the biliary confluence.

Summary of evidence

Unlike fcSEMSs, which can be removed from the duct at the time of surgery, uSEMSs become embedded in the duct wall as a result of tissue and tumor ingrowth. Therefore, the bile duct must be transected above the uSEMS during pancreaticoduodenectomy. To ensure a sufficient length of healthy duct above the point of transection for biliary-enteric anastomosis, the proximal (upstream) end of the stent should be placed at least 1.5 cm below the biliary confluence. In published series and widespread clinical experience, difficulty with dissection and anastomosis of the common duct is not encountered when uSEMSs are placed greater than 1.5 cm below the confluence (149–151).

Recommendation

7. In patients with a malignant extrahepatic biliary stricture that is unresectable or borderline resectable, the evidence is insufficient to recommend for or against uSEMS vs fcSEMS placement.

Summary of evidence

SEMSs are recommended over PSs for the drainage of malignant extrahepatic strictures (see Recommendation 6). Covered SEMSs—referred to in the following sections as fcSEMSs (although some studies evaluated partially covered prostheses)—were developed primarily to prevent ingrowth and thus prolong patency over uSEMSs. To date, at least 10 RCTs have compared fcSEMSs with uSEMSs for distal malignant biliary obstruction. Although earlier and smaller trials tended to favor fcSEMSs (139,152–155), larger RCTs published more recently have demonstrated similar stent patency and patient survival rates between the 2 stent types (156–160). Indeed, the 2 most recent RCTs, comprising 277 patients, have shown either no difference or longer patency associated with uSEMSs (159,160). Two large retrospective cohort studies from major cancer centers including approximately 1,400 patients have also shown no difference in patency and survival (161,162). Meta-analyses published between 2013 and 2021 have consistently affirmed the lack of clear patency advantage associated with covered stents (163–167). Based on available data, this lack of difference in patency appears to be because although fcSEMSs are less likely to permit tumor ingrowth, they are associated with higher rates of tumor overgrowth (around the stent), sludge formation, and stent migration, all of which can lead to recurrent biliary obstruction (164,165).

Acute cholecystitis after SEMS placement across a malignant extrahepatic biliary stricture may occur through 2 proposed mechanisms. The first is compression of the cystic duct and/or its orifice, which may already be compromised by tumor infiltration, by the radial force of the 8–10 mm prosthesis. This phenomenon is hypothesized to occur regardless of whether the SEMS is covered. The second mechanism—unique to fcSEMSs—is direct occlusion of the cystic takeoff by the stent's coating. The risk of cholecystitis after SEMS placement ranges from 5% to 10% (168–171). Whether fcSEMSs are associated with an increased risk of cholecystitis compared with uSEMSs remains uncertain. Randomized trials comparing uSEMSs with fcSEMSs for the relief of malignant extrahepatic biliary obstruction have not demonstrated a statistically significant difference in cholecystitis between groups, although there have been numerically more events in the fcSEMS groups (157,160). Because cholecystitis is an uncommon complication, it is possible that a statistically significant difference in this outcome was not observed because of the low overall event rates in these relatively small randomized trials. Some large cohort studies do suggest that fcSEMSs are independently associated with the development of acute cholecystitis (162,171), whereas others do not (168,170).

Therefore, based on available data, both uSEMSs and fcSEMSs are considered reasonable options for malignant extrahepatic biliary strictures on the basis of equivalent patency and aggregate adverse event rates. Given the potentially increased risk of cholecystitis associated with fcSEMSs, it may be reasonable to favor uSEMSs when the cystic duct takeoff cannot be avoided by the stent.

Drainage: perihilar stricture, benign and malignant

Key concept

9. In patients with obstructive jaundice due to a malignant perihilar stricture who are otherwise asymptomatic and who have declined or are not candidates for additional treatment, palliative drainage is not mandatory and should be decided on an individual case basis.

Summary of evidence

There are no RCTs directly evaluating the clinical outcomes of asymptomatic patients who undergo biliary decompression for a malignant perihilar stricture when they are not candidates for or decline additional treatment. Biliary drainage is often pursued in such patients out of habit and/or to prevent future symptoms or complications, such as pruritus or cholangitis. In addition, a few observational studies have demonstrated that palliative biliary drainage in this context may improve survival (88–90). In 1 study that primarily aimed to compare percutaneous transhepatic biliary drainage (PTBD) with ERCP in patients with Bismuth 3 and 4 strictures who did not undergo surgery or chemoradiotherapy, survival in the group that underwent any form of successful biliary drainage was 8.7 months compared with 1.7 months in the group in which drainage was unsuccessful ($P < 0.001$), and this benefit was maintained in analyses that adjusted for other variables which might affect survival (89). In another retrospective study assessing stenting outcomes in perihilar cholangiocarcinoma, patients who experienced a meaningful reduction in serum bilirubin level after stent placement (to less than or equal to 2 mg/dL or a 50% decrease from the pre-ERCP value) had longer overall survival (hazard ratio 0.57, $P = 0.002$) (90). In addition, effective biliary drainage resulted in significant quality of life benefits, specifically in social function (RR 0.11, 95% CI 0.030–0.19) and mental health (RR 0.036, 95% CI 0.011–0.08), although quality of life metrics did not improve if the serum bilirubin level remained 14 mg/dL or higher (91).

Conversely, drainage is associated with several potential disadvantages that might offset these benefits. First, drainage of perihilar strictures with either ERCP or PTBD increases the risk of cholangitis and biliary sepsis either due to contamination of inadequately drained segments or stent/catheter obstruction (172,173). Given the unique challenges associated with drainage of perihilar strictures, especially in those with more advanced disease, the concern over adverse events is more pronounced in this context than in patients with extrahepatic strictures. In addition, with both ERCP and PTBD, patients are likely to require repeat procedures for stent/drain exchange, which may be burdensome and costly in the final stages of life (174).

When balancing these downsides with the very limited data suggesting a survival advantage, we advise that the potential benefits (prevention of future complications, possible impact on survival and quality of life) and disadvantages (risk of adverse events, increased interaction with the health care system) be thoroughly discussed with patients and their caretakers. Although patients may elect to undergo drainage after this discussion, based on available evidence, ERCP or PTBD is not mandatory in this context.

Recommendation

8. In patients with a perihilar stricture due to suspected malignancy, the evidence is insufficient to recommend for or against ERCP vs PTBD.

Summary of evidence

PTBD and ERCP are widely available and accepted alternatives for the management of malignant perihilar strictures. In the United States, ERCP is generally favored in this scenario based on its high success rates for extrahepatic strictures, the perceived safety and superior tissue sampling capability of ERCP relative to PTBD, the avoidance of external drains that are believed to be undesirable to patients (175), and perhaps because most of these patients are referred to and managed by gastroenterologists. Indeed, a survey of patients and caregivers affected by cholangiocarcinoma revealed that 95% were never given a choice between the 2 alternatives, and the large majority underwent initial ERCP (unpublished data, BJE & Cholangiocarcinoma Foundation).

Only 2 available RCTs inform the decision of whether to recommend ERCP or PTBD as the initial intervention for suspected malignant perihilar stricture. The first is a multicenter trial comparing the 2 modalities in patients with resectable hilar cholangiocarcinoma (176). In this study, trends favoring PTBD over ERCP in terms of technical and clinical success were observed, and >50% of patients in the ERCP group required subsequent PTBD due to inadequate drainage. Despite this, mortality was significantly higher in the PTBD group (RR 3.67, 95% CI 1.15–11.69; $P = 0.03$), resulting in early termination of the trial after 54 patients were randomized (~50% of the original sample size). There was no difference in severe complications (the primary end point) between study groups. Premature termination of this trial has been questioned because neither procedure is considered investigational and the resultant small sample size renders any practice-changing conclusions impossible.

The second was a single-center RCT of ERCP vs PTBD for unresectable perihilar stricture due to gallbladder cancer (177). In this trial, PTBD was associated with a higher rate of successful drainage (defined as bilirubin reduction >50% within 1 week), improved quality of life (contrary to prevailing bias), and fewer complications. There was no difference in mortality. This study, however, was also limited by a small sample size, single-center design, and unblinded adjudication of outcomes.

Observational data are also conflicting. Despite the publication of at least 13 meta-analyses attempting to address this question, clinical decision making in this area remains unclear because the included studies are all retrospective, generally evaluate a small sample at a single center, and compare variable outcomes. In patients undergoing preoperative drainage, at least 3 studies favor ERCP on the basis of improved survival, in part related to reduced seeding metastasis (peritoneal and drain tract) (178–180), whereas at least 4 studies favor PTBD on the basis of higher clinical success, fewer complications, and less conversion to the alternate drainage procedure (181–184). Within the retrospective literature on preoperative drainage, 2 studies were considered of higher methodological quality because of their larger sample size, multicenter design, and inclusion of a Western patient population that would most closely approximate patients seen in the United States (185,186). In these 2 studies, including a combined 518 patients, no difference was observed in any oncological outcomes, including seeding metastasis and recurrence pattern.

Observational studies focusing on unresectable patients or all comers with suspected malignant hilar obstruction are also of low methodologic quality. These retrospective single-center studies, comprising less than 600 total patients, tended to favor PTBD on the basis of increased technical and clinical success and fewer adverse events (89,187,188); however, at least 2 studies showed no difference between the 2 modalities (189,190). The overall pattern of results is congruent with the findings of aforementioned RCT,

which demonstrated better outcomes after PTBD in patients with perihilar stricture due to unresectable gallbladder cancer.

When assessing the data in aggregate, and considering that available RCTs enrolled a total of 108 patients, and also accounting for the heterogeneity and discordance in observational data, we could not find compelling evidence-based rationale to recommend 1 modality over the other, regardless of whether drainage is preoperative or palliative. Thus, until more definitive evidence is available, the choice should be made on an individual basis, considering local practice patterns and patient preferences.

Key concept

10. When ERCP is pursued to diagnose and treat perihilar strictures, it should be performed by endoscopists with sufficient training and/or experience in advanced biliary endoscopy. High-quality ERCP in patients with a perihilar stricture includes preprocedure review of available cross-sectional imaging, careful intraprocedural use of contrast injection and fluoroscopy, and administration of antibiotics when there is concern for slow or incomplete drainage of contrast from opacified bile ducts.

Summary of evidence

Endoscopic drainage of perihilar tumors is considered an advanced ERCP skill (191) and should only be undertaken by those with sufficient training and/or experience in performing therapeutic biliary endoscopy, as advanced techniques will likely be required for diagnosis (e.g., free-hand biopsy and cholangioscopy) and/or drainage (e.g., concurrent parallel or Y-stent deployment). Data on meaningful quality metrics for perihilar biliary interventions are lacking; however, endoscopists and units should formally track or be observant of major procedural outcomes, such as clinical success (i.e., meaningful reduction in bilirubin) and adverse events (192). The adverse events of particular concern when ERCP is performed for perihilar strictures include, but are not limited to, infection (cholangitis, hepatic abscess, and bacteremia), hemorrhage (hemobilia and subcapsular hematoma), bile duct perforation and leak, and maldeployment of uncovered metal stents.

Understanding patterns of normal and variant biliary anatomy is important for optimizing drainage in patients with malignant perihilar obstruction. Preprocedural planning is key, and cross-sectional imaging with contrasted computed tomography or magnetic resonance imaging–magnetic resonance cholangiopancreatography scans should be obtained and reviewed before performing ERCP. Based on radiographic information, a procedural plan that aims to achieve the following goals can be developed: (i) to drain at least 2 sectors of the liver (see key concept 11), including the likely future liver remnant if the patient is a resection candidate; (ii) to avoid opacification of areas into which stent placement is unlikely to be feasible; (iii) to avoid opacification and drainage of atrophic sectors/lobes; and (iv) to drain all substantive ductal systems into which contrast has been injected (whether intentional or not). Foreknowledge of the desired hepatic sector targets can inform initial guidewire passage into that area before injection of contrast, as early nontargeted injection may opacify (and thus contaminate) areas that will ultimately remain undrained, risking segmental cholangitis (193). Opacification and attempted drainage of atrophic sectors is of limited value as stenting of these nonfunctional areas will not contribute to resolution of cholestasis but can lead to cholangitis.

As perihilar endobiliary interventions are often complex, these procedures can require more fluoroscopy than for other ERCPs. Therefore, best practices to reduce radiation exposure to the patient (i.e., use of collimation and the lowest acceptable rate of pulsed fluoroscopy and avoidance of unnecessary magnification and acquisition of extraneous diagnostic spot images) are advisable, which also translate to less radiation exposure to the endoscopy team (194,195).

Generally speaking, antibiotic prophylaxis or treatment is not required in patients without preexisting injection who undergo ERCP that results in complete clearance of injected contrast from the biliary tree. However, incomplete drainage following ERCP is a known predictor of infection and sepsis (193,196). Despite best efforts, some retained contrast is invariably observed after ERCP in patients with complex perihilar strictures. Although in some instances, this may be a reflection of residual contrast within gravity-dependent ducts, whenever there is concern for incomplete or slow drainage of contrast in this context, antibiotic prophylaxis is advisable.

Key concept

11. In patients with a perihilar stricture, hepatobiliary drainage should be pursued in a volumetric sectorial fashion and not in terms of unilateral vs bilateral drainage. The technical goal is to drain >50% of the nonatrophic liver, with each sector contributing roughly one-third of the liver's volume.

Summary of evidence

Whether unilateral or bilateral stent placement is superior in patients with malignant perihilar stricture remains unclear. One randomized trial (197) and 2 meta-analyses (23,198) of bilateral vs unilateral SEMSs for malignant perihilar strictures found no statistically significant difference in drainage success between groups. However, another randomized trial found that bilateral SEMS placement resulted in fewer reinterventions and more durable stent patency in patients compared with unilateral stenting (199). However, the interpretation of studies comparing unilateral vs bilateral stenting has been confounded by heterogeneity in eligible stricture types (some highly cited studies have excluded Bismuth IV tumors (193)), lack of clarity regarding variant biliary anatomy (e.g., drainage of right sectors *via* the left main hepatic duct), varying methods of stent deployment (side-by-side vs stent-in-stent Y configuration), and the use of specialty stents that are not universally available.

Although a considerable amount of effort in the literature has been dedicated to the comparison of unilateral vs bilateral stent placement, it is increasingly accepted that the goal of stenting in patients with perihilar strictures is to drain >50% of the liver's volume (200, 201). In contradistinction to the prior paradigm, which essentially considers the liver as 2 halves (198), current thinking is to approach the liver anatomically in terms of sectorial drainage. Using a sectorial approach, the right anteromedial sector (segments V and VIII), right posterolateral sector (segments VI and VII), and left sector (segments II and III) each account for about 30% of the hepatic volume, and segments I and IV comprise the remaining 10% (201, 202).

To achieve drainage of >50% of the liver, a stent strategy that decompresses at least 2 nonatrophic sectors is required, which might in some cases require a single stent (by, for example, capturing both right anterior and right posterior sectors), 2 stents into the same lobe (by capturing right anterior and right posterior

sectors separately), or bilateral stents (by capturing right posterior and left lateral, for example). It is likely that more reliable success will be achieved using an anatomic sectorial approach as opposed to a unilateral vs bilateral approach. One retrospective study found that soft multifenestrated PSs or open-cell uSEMSs were similarly effective and relieving jaundice when a targeted sectorial approach for ERCP-directed biliary drainage was used (201).

On this basis, we have elected not to provide a recommendation on the question of unilateral vs bilateral stent placement for the drainage of malignant perihilar strictures but rather to highlight the importance of a paradigm shift toward a sectorial drainage strategy in clinical practice and in future research.

Recommendation

9. In patients with a malignant perihilar stricture, the evidence is insufficient to recommend for or against PS vs uSEMS placement.

Summary of evidence

Three randomized trials, including 199 patients, and several large cohort studies have consistently found that in patients with unresectable malignant perihilar biliary obstruction, primarily from cholangiocarcinoma, transhilar uSEMS is associated with longer stent patency compared with placement of PS (203–209). In addition, one of the RCTs showed a survival benefit (203) and another a trend toward increased survival (205) in the SEMS group. A meta-analysis that included both prospective and retrospective studies demonstrated superior stent patency of SEMSs over PSs but did not confirm a survival advantage (23). In this meta-analysis, SEMSs were associated with a lower 30-day (OR 0.16; 95% CI 0.04–0.62) and long-term (OR 0.28; 95% CI 0.19–0.39) occlusion rate compared with PSs in patients with malignant perihilar strictures.

Caution, however, should be exercised when applying these data to clinical practice for several reasons. First, scheduled exchange of PSs was not permitted in the RCTs, which biases in favor of the uSEMS group and is not reflective of routine clinical practice in the United States. Second, only 10-mm uSEMSs were used in the RCTs with very high technical success rate, which is also atypical for routine practice wherein 6–8 mm uSEMSs are often needed for this indication. Finally, available studies included patients who were treated with strategies that would be considered unconventional in US endoscopic practice, such as *via* PTBD or through a staged process with initial nasobiliary tube placement (197,205).

Two other important considerations should inform the decision of plastic vs metallic stents for malignant perihilar stricture. The first is that many patients with unresectable perihilar strictures who receive palliative uSEMSs will outlive the patency of their metal stent(s) and repeat ERCP or salvage PTBD may be required. Endoscopic reintervention to reestablish drainage through multiple occluded uSEMSs is particularly challenging and may result in an increased need for PTBD over a strategy of routine PS exchanges (210). As such, patients should be informed that uSEMSs cannot be removed and may make subsequent endoscopic biliary intervention more challenging or impossible. This discussion and shared decision making, particularly in patients with good functional status, may lead some patients, caregivers, and endoscopists to favor replaceable PSs. The second consideration is that intraductal ablative therapies to prolong survival in patients with cholangiocarcinoma are typically applied programmatically at the time of PS exchange (see Recommendation 10). The efficacy of these therapies, particularly radiofrequency ablation (RFA)—which requires direct electrode contact with the tumor—through a metallic stent is unknown. Furthermore, the value of uSEMSs (which is to limit the number of additional ERCPs) is not realized if the patient has to return on a scheduled basis to undergo intraductal therapy. Thus, PSs are favored in patients who have elected to undergo these therapies as part of their oncologic treatment plan. Therefore, even though the existing literature supports the use of uSEMS over PS for malignant perihilar strictures, concerns about the applicability and generalizability of research findings to clinical practice, as well as considerations related to reintervention in the growing number of patients who outlive their uSEMS and the role of intraductal ablative therapies, influence the guidance that both PS and uSEMS are reasonable options that can be used selectively based on clinical and anatomic factors as well patient and caregiver preferences.

Key concept

12. If SEMS is chosen for drainage of a malignant perihilar stricture, an effective drainage strategy using PS should be proven first.

Summary of evidence

The merits and disadvantages of plastic and metallic stents for the drainage of malignant perihilar strictures are discussed above in Recommendation 9. However, when SEMSs are chosen in this context, it is important to consider that intrahepatic bile ducts upstream of a perihilar stricture are often smaller with a more complex branching patterns, and therefore, uSEMSs are typically necessary (relative to covered SEMSs) because they are available in smaller sizes and do not jail off secondary and tertiary branch ducts. However, uSEMSs become permanently embedded into the duct wall and cannot be removed or repositioned in the event of inadequate initial drainage, which may occur in up to 40% of cases (211). Endoscopic reintervention to achieve more complete drainage through uncovered stents is particularly challenging, likely resulting in an increased need for percutaneous salvage (210). Therefore, if uSEMSs are chosen for the drainage of malignant perihilar stricture that is characterized as Bismuth type II–IV, we suggest that PSs be placed first to confirm that the positioning of the stents captures sufficient liver volume to allow resolution of jaundice. Once an effective drainage strategy has been proven, the PS(s) can be replaced by SEMSs with high confidence that additional interventions in the short term will not be necessary.

Drainage: additional considerations for extrahepatic and perihilar strictures

Recommendation

10. In patients with a malignant perihilar stricture due to cholangiocarcinoma who are not candidates for resection or transplantation, we suggest the use of adjuvant endobiliary ablation (photodynamic therapy [PDT] or RFA) plus PS placement over PS placement alone (conditional recommendation, low-quality evidence).

Summary of evidence

PDT and RFA are commercially available ablative techniques that can be applied *via* PTBD or ERCP to treat patients with

unresectable malignant biliary strictures (202). In PDT, a laser fiber is used to diffuse light of a specific wavelength that activates a photosensitizer that has been infused intravenously in advance of the ERCP. This activation generates reactive oxygen species that destroy tumor cells directly. The laser light can also refract through bile to treat tumor cells that are distant to the location of the activated fiber. ERCP-directed RFA uses bipolar electrodes to deliver thermal energy that produces coagulative necrosis of the portion of the stricture that is in direct contact with the catheter. In both treatment modalities, it is hypothesized that injury to the tumor and tumor-associated vasculature with subsequent dissemination of tumor fragments into the circulation can result in stimulation of an immune response against the malignancy (212). This phenomenon may explain why some studies have observed a survival benefit despite no difference in biliary patency (213).

Two small but seminal RCTs demonstrated a statistically significant survival advantage (13–14 months) in patients with unresectable perihilar biliary malignancies who underwent PDT using porfimer sodium photosensitizer (214) or a second-generation hematoporphyrin derivative photosensitizer that is not available in the United States (215). Larger retrospective studies have also demonstrated a survival advantage when PDT and stent replacement was compared with stent replacement alone, although some of these studies included patients who underwent PDT *via* PTBD (216–218). Three meta-analyses published over a 5-year span, that included these randomized and observational data, found significantly longer survival associated with the addition of PDT to programmatic stent exchange in patients with inoperable cholangiocarcinoma (219–221), and 2 of these showed improvement in patient performance status (219,221).

The published literature evaluating endobiliary RFA plus biliary stent placement vs stenting alone in patients with malignant biliary obstruction also supports a survival advantage. Two RCTs from China that included a total of 239 patients with mostly malignant extrahepatic and some perihilar (~30%) strictures showed statistically significant improvements in survival associated with RFA but had divergent results in terms of stent patency (213,222). Importantly, one of these studies excluded patients with Bismuth IV tumors (213) and the other excluded patients with Bismuth III and IV tumors (222). Comparative retrospective cohort studies have also included heterogeneous patient populations but have demonstrated consistently favorable outcomes associated with RFA (223–226). Three meta-analyses have affirmed a survival benefit associated with endobiliary RFA compared with a strategy of stent exchange alone (227–229). It is important to consider that most studies evaluated the effect of repeated ablation sessions at the time of routine stent exchange. RFA as a 1-time treatment before metallic stent placement was shown to improve survival in a small observational study (230); however, a small phase II RCT showed no benefit associated with this approach (231).

Meta-analyses of both PDT and RFA demonstrate favorable safety profiles compared with biliary decompression alone, although RFA does result in increased postprocedure abdominal pain and has been implicated in the development of hemobilia in approximately 4% of cases, sometimes due to arterial pseudoaneurysm formation given the proximity of the biliary confluence to the hepatic vasculature (228). PDT results in photosensitivity that mandates patients avoid direct and indirect sunlight for 4–6 week after the procedure to avoid severe cutaneous burns (202).

Limited data suggest that PDT and RFA may be comparably efficacious in treating patients with perihilar cholangiocarcinoma (232). However, our interpretation of the literature is that the overall strength of evidence supporting PDT in patients with perihilar cholangiocarcinoma is greater than that for RFA. An important consideration in applying the RFA literature to perihilar strictures is the heterogeneity of study samples in randomized and observational studies, wherein most patients had extrahepatic rather than perihilar strictures. Nevertheless, the number of patients with perihilar strictures in available RFA RCTs is similar to the number of patients with cholangiocarcinoma included the PDT RCTs, justifying a conditional recommendation on the basis of low-quality evidence. Additional prospective and methodologically rigorous research focused on RFA for perihilar strictures is necessary to refine our estimates of benefit. This research is of particular importance because the greater of ease of application, lower cost, FDA approval (compared with PDT photosensitizers that are not FDA approved for treatment of cholangiocarcinoma), and lack of photosensitivity make endobiliary RFA more appealing to endoscopists and patients.

In general, both PDT and RFA are best initiated after multidisciplinary evaluation to confirm inoperability, as the full-thickness injury (by RFA in particular) may lead to tissue edema and scaring that confounds subsequent preoperative imaging and complicates decision making around surgical candidacy. Given these considerations, and the likely need to apply RFA at the time of the initial diagnosis of malignant extrahepatic strictures (before the metallic stent is placed), additional research is needed to clarify the role of intraductal ablation for extrahepatic cancers.

Recommendation

11. In patients with a biliary stricture, in whom ERCP is indicated but unsuccessful or impossible, we suggest EUS-guided biliary access/drainage over PTBD, based on fewer adverse events, when performed by an endoscopist with substantial experience in these interventional EUS procedures (conditional recommendation, very-low-quality evidence).

Summary of evidence

Cannulation of the bile duct is unsuccessful in up to 8% of ERCP cases (233, 234). The traditional salvage option for biliary drainage after unsuccessful or impossible ERCP has been PTBD, although EUS-guided intervention has emerged as a viable alternative. EUS-guided access to facilitate ERCP can be achieved through the rendezvous technique, wherein the intra- or extrahepatic bile duct is punctured with an FNA needle, permitting antegrade passage of a guidewire through the papilla (or biliary-enteric anastomosis) to facilitate subsequent cannulation. Alternatively, biliary drainage can be achieved directly with the echoendoscope by stent placement over a guidewire across the transmural tract that is created between the GI lumen and bile duct (choledochoduodenostomy or hepaticogastrostomy) or antegrade across the stricture/papilla using the lumen-duct fistula as an access point. Various techniques and procedural algorithms have been described.

Meta-analyses evaluating EUS-guided biliary access and drainage—each comprising 500–1,500 cases—suggest that these interventions are associated with a technical success rate of approximately 90% and an adverse event rate of 15%–20% (235–237). Although most adverse events appear to be mild, severe complications and related fatalities have been reported, especially earlier in the learning curve (238–240); these appear to be lowest with the rendezvous technique (241) and higher after hepaticogastrostomy (242, 243). Studies included in the aforementioned meta-analyses

are heterogeneous in terms of indications, techniques, and stent selection.

Two published randomized trials, including a total of 91 patients, have compared EUS-guided drainage with PTBD in cases of unsuccessful biliary cannulation during ERCP (244,245). Most patients included in these trials had extrahepatic biliary stricture due to malignancy and were drained *via* EUS-guided choledochoduodenostomy. Both studies demonstrate similar technical and clinical success rates between the 2 drainage options, but one observed significantly less complications and reinterventions in the EUS group (245). Interestingly, neither study demonstrated a quality of life benefit associated with internal drainage. In aggregate, observational comparative studies have generally shown similar findings (246–249). Not surprisingly, a meta-analysis that includes the 2 aforementioned RCTs and another trial published only in abstract form as well observational studies affirms that EUS-guided intervention is of equivalent efficacy to PTBD but may be substantially safer and require far fewer interventions (250).

Therefore, on the basis of limited randomized and broader observational data, it does appear that EUS-guided access and drainage may be preferred over PTBD. However, it is important to reiterate that severe and fatal complications have been reported and that randomized trials addressing this question have included only less than 100 participants. Furthermore, it is worth highlighting that investigators who conduct early studies in a novel area tend to have higher levels of expertise and experience and more conflict of interest (intellectual and commercial), leading to results that might overestimate success and underappreciate risk. Thus, the use of these procedures as an alternative to PTBD after unsuccessful ERCP should be reserved for endoscopists with substantial training and/or experience in performing EUS-guided interventions. More widespread diffusion of these procedures in clinical practice will require the development of dedicated instruments for interventional EUS and research of broader generalizability. It is also important to consider that repeat ERCP after unsuccessful cannulation by the same or different provider on a subsequent day is successful in the large majority of cases and represents a reasonable alternative to both EUS-guided drainage and PTBD in patients who do not require urgent decompression (251–253).

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CONFLICTS OF INTEREST

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