Management of Biliary Strictures After Liver Transplantation

Nicolas A. Villa, MD, and M. Edwyn Harrison, MD

Dr Villa is an advanced endoscopy fellow and Dr Harrison is a professor in the Division of Gastroenterology and Hepatology at the Mayo Clinic in Scottsdale, Arizona.

Address correspondence to:
Dr M. Edwyn Harrison
13400 East Shea Boulevard
Scottsdale, AZ 85259
Tel: 480-301-4914
E-mail: Harrison.M@mayo.edu

Abstract: Strictures of the bile duct are a well-recognized complication of liver transplant and account for more than 50% of all biliary complications after deceased donor liver transplant and living donor liver transplant. Biliary strictures that develop after transplant are classified as anastomotic strictures or nonanastomotic strictures, depending on their location in the bile duct. The incidence, etiology, natural history, and response to therapy of the 2 types vary greatly, so their distinction is clinically important. The imaging modality of choice for the diagnosis of biliary strictures is magnetic resonance cholangiopancreatography because of its high rate of diagnostic accuracy and limited risk of complications. Biliary strictures that develop after liver transplant may be managed with endoscopic retrograde cholangiography (ERC), percutaneous transhepatic cholangiography (PTC), or surgical revision, including retransplant. The initial treatment of choice for these strictures is ERC with progressive balloon dilation and the placement of increasing numbers of plastic stents. PTC and surgery are generally reserved for failures of endoscopic therapy or for anatomic variants that are not suitable for ERC. In this article, we discuss the classification of biliary strictures, their diagnosis, and the therapeutic strategies that can be used to manage these common complications of liver transplant.

Keywords
Anastomotic strictures, nonanastomotic strictures, endoscopic retrograde cholangiography, deceased donor liver transplant, living donor liver transplant, biliary stenting, biliary dilation

Biliary strictures are a well-known and common complication of both living donor liver transplant (LDLT) and deceased donor liver transplant (DDLT) and account for more than 50% of all biliary complications of liver transplant.[1-3] The factors that most commonly contribute to stricture formation include the surgical reconstruction technique (eg, duct-to-duct anastomosis vs choledochojejunostomy), use of a T-tube, type of liver transplant procedure (LDLTs are more prone to strictures than DDLTs), and development of hepatic arterial thrombosis. Biliary strictures are classified as anastomotic strictures or nonanastomotic strictures, depending on their location.

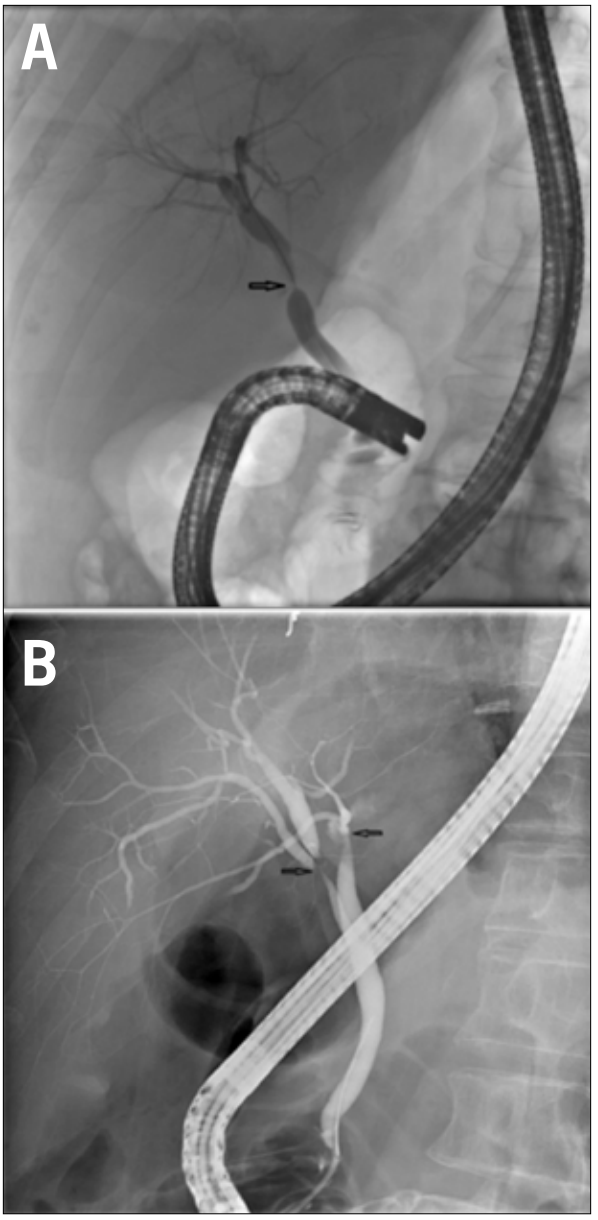

Figure 1. Cholangiograms of anastomotic strictures in a deceased donor liver transplant (arrow, **A**) and a living donor liver transplant (arrows, **B**).

In the early surgical experience, the incidence of biliary strictures after liver transplant was reported to be as high as 60%.[4] With improvements in organ selection, retrieval, and preservation as well as the standardization of biliary reconstruction techniques, the incidence of biliary strictures has been reduced dramatically to less than 16% overall.[5-8] In a meta-analysis involving more than 14,000 patients, the incidence of anastomotic strictures was reported to be approximately 13%.[9] The incidence of nonanastomotic strictures is considerably lower (4%-10% in 2 studies).[8,10]

Biliary strictures can occur months to years after liver transplant, but they most commonly present within the first year, with a mean interval from transplant to time of presentation of 5 to 8 months.[11-13] Strictures that occur early after liver transplant usually result from technical problems in the surgery itself, whereas strictures that develop later arise mainly from vascular insufficiency, immunologic causes, or problems with healing and fibrosis.[14-16]

Although biliary strictures account for significant morbidity and mortality after liver transplant, advances in endoscopic therapy and interventional radiology have improved outcomes by decreasing the need for surgical repair or retransplant, both of which carry much higher morbidity and mortality rates. Currently, the first line of treatment for biliary strictures is endoscopic therapy. In this article, we discuss the classification of biliary strictures, their diagnosis, and the strategies used to treat them.

Classification

Biliary strictures are classified as anastomotic or nonanastomotic, depending on their location. Their incidence, etiology, natural history, and response to therapy differ greatly, so the distinction between the 2 types of strictures is clinically important.

Anastomotic Strictures

Anastomotic strictures are defined as segmental or focal narrowings around a biliary anastomosis and are thought to result primarily from fibrotic healing (Figure 1).[17] Anastomotic strictures are more common than nonanastomotic strictures, are localized at the site of anastomosis, and are single, focal, and short.[1,18,19]

Before the 1990s, anastomotic strictures affected approximately a third of patients.[4,19,20] With the advent of improved techniques, the overall incidence of anastomotic strictures is reported to be approximately 13%; strictures at the biliary anastomosis develop after DDLT in 12% of patients (range, 5%-15%) and following LDLT in 19% (range, 13%-36%).[9,12,21-24] The higher incidence of strictures after LDLT is explained by the necessity for resecting a portion of the donor liver rather than using the entire organ, as is possible with DDLT. With resection of the donor graft in LDLT, there is a risk of devascularization of the bile duct at the hilar dissection and the potential for bile leakage from the cut surface, causing fibrotic changes around the anastomosis. The use of a partial liver for the graft also frequently results in the requirement for multiple anastomoses of smaller bile ducts.[25-27]

The onset of anastomotic strictures ranges widely, with strictures diagnosed from 7 days to 11 years after transplant, according to a meta-analysis.[9] Although anastomotic strictures can present at widely variable times, the

Table. Most Common Risk Factors for the Development of Anastomotic Strictures After Liver Transplant

DDLT	LDLT	Both DDLT and LDLT
Female donor	Advanced donor age	Advanced recipient age
Failure to flush the donor duct	Multiple anastomoses	Preceding bile leakage
Acute or chronic rejection	Long cold and warm ischemia times	Small caliber of the bile ducts[a]
Choledochojejunostomy reconstruction	Hepatic artery thrombosis	Inappropriate suture material[a]
Hepaticojejunostomy reconstruction	Duct-to-duct reconstruction	Tension at the anastomosis[a]
		Improper surgical technique[a]

[a] Technical issues leading to anastomotic strictures in both DDLT and LDLT.

DDLT, deceased donor liver transplant; LDLT, living donor liver transplant.

majority occur within the first year after transplant.[6,11,19] However, it also appears that the incidence increases with longer follow-up, as the cumulative risk of anastomotic strictures at 1, 5, and 10 years after transplant is 6.6%, 10.6%, and 12.3%, respectively.[18]

Risk factors associated with the development of anastomotic strictures are numerous and include recipient, graft, operative, and postoperative factors. The contributions of these risk factors differ between patients undergoing DDLT and those undergoing LDLT (Table). The most common risk factors for anastomotic strictures in patients undergoing DDLT are advanced recipient age, female donor, failure to flush the donor duct, preceding bile leakage, acute rejection, chronic rejection, and choledochojejunostomy or hepaticojejunostomy reconstruction rather than duct-to-duct reconstruction.[18,19,28-31] The most common risk factors for anastomotic strictures in LDLT are advanced recipient age, advanced donor age, more than 1 biliary anastomosis, longer cold and warm ischemia times, preceding bile leakage, hepatic artery thrombosis, and duct-to-duct reconstruction rather than hepaticojejunostomy reconstruction.[23,32-39] Technical issues may be responsible for anastomotic strictures in both DDLTs and LDLTs, including improper surgical technique, small caliber of the bile ducts, inappropriate suture material, and tension at the anastomosis.[40] As a general rule, anastomotic strictures that appear early in the postoperative period are usually secondary to surgical technical issues or postoperative bile leak, whereas those that appear later are most likely due to fibrotic healing arising from ischemia at the end of the donor or recipient bile duct.[13,15,18]

Nonanastomotic Strictures

A nonanastomotic stricture is defined as 1 or more focal areas of narrowing of the bile ducts proximal to a biliary anastomosis,[11,12] and often occurs at multiple sites. These strictures are longer and occur less frequently and earlier than anastomotic strictures, with a mean time to stricture formation of 3 to 6 months.[8,10,12] The overall incidence of nonanastomotic strictures has been reported to be from 4% to 10%.[8,10] It is thought that these strictures develop as a result of ischemia and immunologic events. The primary risk factors for ischemic strictures include hepatic artery thrombosis, chronic ductopenic rejection, blood type ABO incompatibility, and a diagnosis of primary sclerosing cholangitis before transplant.[5,10,41,42] Studies also have suggested that a pretransplant diagnosis of autoimmune hepatitis, prolonged warm and cold ischemia times, donation after cardiac death, and prolonged donor use of vasopressors are independent risk factors for nonanastomotic stricture formation.[10,43,44]

Nonanastomotic strictures are commonly associated with secondary problems. Because of the presence of multiple strictures that frequently involve both the intra- and extrahepatic ducts, and the associated impairment of bile outflow, biliary sludge may accumulate proximal to the strictures, leading to the formation of calculi.[5] Biliary casts that follow the contour of the bile ducts may also develop. These most likely result from sloughing off of biliary epithelium as a result of ischemic or immunologic injury, infection, or bile stasis.[5,45] The formation of intraductal calculi and biliary casts, and the presence of multiple strictures, can create technical challenges to effective endoscopic therapy.

Surgical Reconstruction Techniques and the Risk of Strictures

Surgical advances in liver transplant have reduced the frequency of biliary complications. Technical advances include the standardization of effective techniques, such as resection of the gallbladder of the donor liver, and the abandonment of procedures more frequently associated with complications, such as cholecystoduodenostomy and cholecystojejunostomy, in favor of choledochocholedochostomy and Roux-en-Y choledochojejunostomy.[19] Improvements in suturing techniques for creating the duct-to-duct anastomosis have also been described, such as the use of interrupted sutures in place of continuous sutures.[46] At present, the 2 most common methods for biliary reconstruction during liver transplant are duct-to-duct anastomosis and bilioenteric anastomosis with a Roux-en-Y loop. The latter can be further divided into hepaticojejunostomy and choledochojejunostomy.

Duct-to-Duct Vs Bilioenteric Anastomosis

The duct-to-duct anastomosis is the biliary reconstruction of choice in patients with healthy native bile ducts because it preserves the physiologic bilioenteric cycle, prevents enteric reflux into the bile ducts, and facilitates access to the biliary system by endoscopic means if biliary complications develop.[12,19,30,35,47,48] In addition, this technique is technically easier and requires less operative time than the construction of a bilioenteric anastomosis. With the improvement of surgical techniques, the duct-to-duct anastomosis also has evolved to become the preferred reconstruction method for LDLT, despite its greater challenges technically.[19,46,49] LDLT is associated with more complex bile duct anatomy, so successful biliary reconstruction requires the creation of multiple biliary anastomoses in which the recipient right and left hepatic ducts and often the recipient cystic duct are used to adequately drain the intrahepatic ducts of the donor graft.[22,50]

Biliary anastomosis with the Roux-en-Y jejunal limb is performed primarily in patients with preexisting disease of the native biliary tract, such as primary sclerosing cholangitis. The hepaticojejunostomy or choledochojejunostomy anastomosis is also used when there is a marked discrepancy between the sizes of the donor and recipient bile ducts, when the bile duct is unavailable (eg, biliary atresia), and during retransplant when the length of the native biliary system is inadequate. Roux-en-Y limbs were more frequently used in the early years of LDLT, before expertise in complex biliary reconstruction was acquired.[51-54]

In a meta-analysis of 14,359 liver transplants (11,547 DDLTs and 2812 LDLTs), duct-to-duct reconstruction was the procedure of choice for all patients undergoing transplant and was performed in 88% of patients. The preference for duct-to-duct anastomosis was particularly strong in DDLT cases; duct-to-duct anastomosis and bilioenteric anastomosis were performed in 92% and 8% of DDLT cases, respectively. In LDLT cases, duct-to-duct anastomosis remained the predominant choice, but bilioenteric anastomosis was used more frequently, with duct-to-duct anastomosis and bilioenteric anastomosis performed in 69% and 31% of cases, respectively.[9] Although duct-to-duct anastomosis is now generally the preferred method of reconstruction, some institutions continue to use the bilioenteric method for patients undergoing LDLT.

Use of T-Tubes

The use of a T-tube in transplant reconstruction remains controversial; however, in practice, its routine use has largely been abandoned. During the early years of liver transplant, T-tubes were commonly used during duct-to-duct reconstruction as a means to protect against anastomotic stricture formation, to help monitor liver function by assessing the flow and color of bile, and to allow the convenient performance of cholangiography when necessary.[20,55,56] The use of a T-tube has declined to fewer than 20% of liver transplants in the current era.[9] T-tubes are used infrequently because of an increased risk of biliary complications, including bile leaks around the tube, cholangitis, and acute bile peritonitis after T-tube removal, as well as increased costs of management.[57-59]

Interestingly, studies from several centers have presented opposing data showing that the use of a T-tube is associated with a decreased risk of biliary anastomotic stricture formation without an increase in the incidence of other biliary complications.[9,60,61] The use of internal stents theoretically might eliminate the complications associated with T-tubes while maintaining the benefits of a splint, but their deployment has not shown consistent benefit.[62-65]

Sphincter of Oddi Dysfunction

The sphincter of Oddi regulates the flow of bile and pancreatic secretions through the ampulla of Vater into the duodenum. Sphincter of Oddi dysfunction (SOD) is a clinical syndrome resulting from elevated sphincter pressure that is characterized by abdominal pain, bile duct dilatation, and elevated serum liver chemistries in a cholestatic pattern. At the time of liver transplant, denervation of the common bile duct can lead to the development of a hypertonic sphincter and the secondary development of SOD with biliary or pancreatic obstruction. SOD has a low prevalence of 2% to 7% after liver transplant.[66,67]

When T-tubes were used routinely after liver transplant, bedside measurement of the resting bile duct pressure could be used as a screening tool for SOD.[68] Without the routine use of T-tubes, clinical vigilance is required to detect this uncommon complication. SOD should be suspected in patients with elevated serum liver chemistries and a diffusely dilated bile duct without filling defects or significant strictures that might cause obstruction or acute pancreatitis in the postoperative period without other explanation. Abdominal pain is not required for a diagnosis of SOD in this context. The benefit of using biliary manometry in the diagnosis of SOD after transplant is uncertain. The management of SOD after transplant is straightforward; it is treated effectively with endoscopic sphincterotomy.

Diagnosis

Clinical Presentation

The clinical presentation of patients with biliary strictures after liver transplant is generally the result of obstruction to bile outflow, although cholangitis can supervene in a minority of cases.[57,67] The clinical findings can include jaundice, right upper quadrant pain, fever, and pruritus. The liver profile may be elevated in

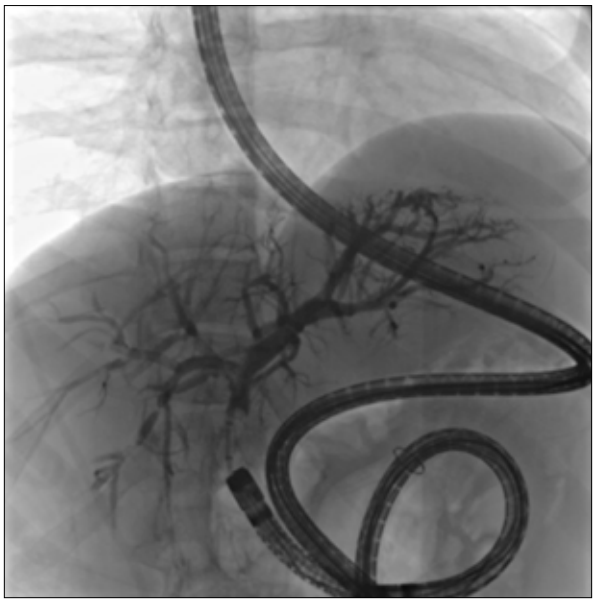

Figure 2. A cholangiogram showing access to a hepaticojejunostomy through single-balloon enteroscopy.

a cholestatic pattern, with elevated alkaline phosphatase and γ-glutamyltransferase levels, elevated direct bilirubin levels, and mildly to moderately elevated transaminase levels.[69-71] The diagnosis occasionally can be challenging because of overlapping clinical signs and symptoms in patients with acute or chronic rejection, hepatic artery stenosis or thrombosis, or systemic infections that do not involve the hepatobiliary tract but do produce secondary changes of cholestasis. Uncertainty in the diagnosis may lead to unnecessary procedures, with substantially increased risks of iatrogenic complications for the patient. The onset of symptoms can vary from a few days to more than 10 years after liver transplant but generally occur within the first year.[9]

Imaging Modalities

The diagnosis of biliary strictures after transplant may be achieved through the use of a variety of imaging modalities, including ultrasound (US), magnetic resonance imaging (MRI), endoscopic retrograde cholangiography (ERC) or percutaneous cholangiography (PTC), and hepatobiliary iminodiacetic acid (HIDA) scan. US is commonly the first study used because it is widely available and relatively inexpensive, and it can provide cross-sectional images as well as information regarding the hepatic vasculature. US imaging with Doppler can provide good information about the flow characteristics of all components of the hepatic vasculature, including the hepatic artery and the portal and hepatic veins, allowing the exclusion of hepatic arterial and venous disorders. US also is accurate in detecting changes in the caliber of the biliary system, although its sensitivity in the detection of bile duct obstruction in patients with a liver transplant is relatively low, ranging between 38% and 66%.[72] Dilatation is not a consistent finding in patients with biliary obstruction after transplant, and biliary obstruction from a bile duct stricture without associated dilatation is not readily detected by US.[73] It has been suggested that biliary fibrosis after transplant causes the donor bile ducts to become less pliable, with a diminished capacity to dilate during distal obstruction.

MRI with magnetic resonance cholangiopancreatography (MRCP) is used with increasing frequency after liver transplant. MRI provides excellent cross-sectional imaging of the liver and intra-abdominal structures, allowing the detection of a variety of postoperative problems. MRI with MRCP is the most effective noninvasive imaging modality for the assessment of biliary complications after liver transplant.[40] This modality has a sensitivity of 95% and an overall accuracy of 95%, with ERC used as the gold standard.[74] MRI with MRCP has become the imaging modality of choice to detect a posttransplant biliary stricture before direct endoscopic or percutaneous cholangiography and is usually the second test ordered after US.

Direct cholangiography through ERC and PTC remains the gold standard for the diagnosis of biliary strictures after liver transplant. These procedures are typically not used for diagnostic purposes alone but more often when definitive therapy is needed because of their relatively high risk of complications. However, one study demonstrated that ERC can be used effectively for initial diagnosis as well as treatment in patients who are at high risk of biliary disease on the basis of suggestive clinical findings.[75]

ERC is recommended over PTC when technically feasible because ERC is less invasive, preferred by patients, often more efficacious, and associated with significantly lower rates of complications.[3,76] PTC is generally reserved for patients in whom ERC has failed, or for patients with a hepaticojejunostomy or choledochojejunostomy and Roux-en-Y anastomosis. Centers with experience in balloon-assisted enteroscopy may attempt ERC for patients with Roux-en-Y anatomy in place of PTC, using single- or double-balloon enteroscopy to achieve access through the Roux limb to the hepatobiliary anastomosis (Figure 2).[77,78] However, balloon-assisted enteroscopy often fails to achieve biliary access in these patients, even in experienced hands. The technical difficulty of balloon-assisted enteroscopy, the additional expertise required, and the extended duration of the procedure, together with the associated risks of anesthesia and increase in costs, should be weighed against the proven alternative of PTC for patients with altered surgical anatomy.

Hepatobiliary scintigraphy (HIDA scan) with technetium-99m iminodiacetic acid is not commonly used to

diagnose biliary strictures after liver transplant, but it is important to note that it has 75% sensitivity and 100% specificity for the diagnosis of biliary obstruction and is a useful test for the diagnosis of biliary leaks. At present, this test is used mostly for the detection of biliary leaks.[79]

Therapy

The management of biliary strictures after liver transplant can be divided into 3 therapeutic strategies: ERC-guided therapy, PTC-guided therapy, and surgical revision, including retransplant.

Endoscopic therapy is currently the first-line approach to the treatment of posttransplant biliary strictures. ERC is widely available and effective, and it has relatively limited complications in comparison with PTC-guided therapy or surgical revision.[12,76] Nonetheless, PTC-guided therapy and surgical revision are still used as first-line treatment strategies in as many as 15% and 4% of institutions, respectively. Surgical reconstruction by Roux-en-Y hepaticojejunostomy once was the management of choice for strictures after liver transplant, but now it is primarily used as rescue therapy for patients in whom ERC- or PTC-guided therapy has failed. The most aggressive surgical solution, retransplant for the salvage treatment of biliary strictures, is now rare and performed in fewer than 1% of cases.[9]

Endoscopic Retrograde Cholangiography–Guided Therapy

ERC-guided therapy for biliary strictures after liver transplant is indicated when a patient shows symptoms or signs of biliary obstruction and imaging studies show evidence of bile duct strictures. Endoscopic intervention generally is not performed for incidental findings of biliary narrowing on imaging in asymptomatic patients with stable liver test values, although patients with these clinically insignificant strictures should be followed closely for evidence of worsening biliary obstruction over time. ERC occasionally can be used as a diagnostic test in symptomatic patients in whom there is no other explanation for cholestasis, even in the absence of biliary dilatation, because strictures can be missed by cross-sectional imaging modalities and the bile ducts do not reliably dilate in response to obstruction after transplant.

The overall success rates for the endoscopic therapy of biliary strictures after liver transplant are very good. Sustained patency is reported in 57% to 90% of patients with anastomotic strictures after DDLT, with the most recent studies reporting even higher success rates of 80% to 90%.[9,18,70,80] Endoscopic treatment for anastomotic strictures after LDLT is also effective, although reports do show somewhat lower rates of stricture patency of 60% to 84%.[24,36,81-83] The generally high rates of success in the treatment of biliary strictures after transplant are due to improvements in endoscopic techniques.

Anastomotic Strictures After Deceased Donor Liver Transplant The majority of studies evaluating the treatment of biliary strictures after liver transplant have focused on patients with anastomotic strictures after DDLT. Treatment has evolved from the simple dilation of strictures to a series of ERC procedures in which stricture dilation is followed by the placement of a progressively larger number of plastic stents or self-expandable metal stents (SEMS).

Balloon Dilation Alone Balloon dilation alone without stent placement offered a straightforward and relatively noninvasive treatment for anastomotic strictures after DDLT, but results were compromised by the frequent recurrence of strictures and a long-term success rate of only 30% to 40%.[71,84] Because of the higher success rates achieved with balloon dilation followed by stent placement, this practice has largely supplanted balloon dilation alone.

Balloon Dilation and Plastic Stent Placement Balloon dilation with multiple stent placement has become the standard of care for anastomotic strictures after DDLT. Although this approach typically requires a series of ERC procedures over a course of 6 to 12 months, endoscopic treatment is generally well tolerated and the benefit durable. Balloon dilation with plastic stent placement for anastomotic strictures after DDLT achieves a long-term patency rate in the range of 75% to 90%.[71,84]

Several endoscopic techniques have been used after DDLT to achieve the sustained dilation of anastomotic strictures. Balloon dilation of the biliary stricture followed by the placement of two 10-French (Fr) plastic stents and replacement of the stents at 3-month intervals achieved good long-term success rates; sustained patency of the strictures was achieved in 74% to 90% of cases at 1 year after treatment.[85-87] The placement of progressively greater numbers of stents at each ERC procedure after balloon dilation achieved even higher rates of stricture patency, with reported sustained patency rates of 88% to 100% at the end of treatment and long-term rates of 82% to 89% after at least 12 months of follow-up.[14,80,85] In one study in which progressively more stents were placed at each intervention, the mean number of stents placed at the last intervention was 3.2 (range, 1-6), and the mean duration of treatment was 12 months (range, 2-24 months).[85] In another study of progressive stenting, the mean duration of endoscopic treatment was considerably shorter, 4.6 months. The shortest reported duration of stenting was 3.5 months, and this was achieved by using progressive stenting in combination with very short intervals between each endoscopic intervention.[14] In another study, per-

forming ERC every 2 weeks achieved a sustained patency rate of 87%, with a mean number of ERC procedures of 3.4 (range, 2-6), mean maximal number of stents inserted of 2.5 (range, 1-6), and mean total stenting period of 107 days (~3.5 months).[80]

Anastomotic biliary strictures that develop early after liver transplant may be more responsive to endoscopic treatment than strictures that develop 6 months or more after transplant. Strictures that occur within the first month after transplant may be caused by transient inflammation, postoperative edema, or technical issues. When feasible, delayed endoscopic intervention, which allows healing of the anastomosis, is preferable to subjecting a fresh anastomosis to dilation and stenting. If intervention is required during the first month postoperatively because of symptomatic cholestasis or cholangitis, then a 7- or 8.5-Fr stent can be placed without dilation, and dilation can be deferred to the next intervention. When the stricture is too tight to allow stent placement, we have found that dilation with a 4-mm balloon typically can be tolerated, although the risk of rupture of the anastomosis and bile leak cannot be overlooked. Smaller balloons developed for angioplasty also are available and may be helpful for particularly tight biliary strictures.[88] No data regarding the use of dilating biliary catheters in posttransplant anastomotic biliary strictures are available, but a small dilating catheter may be a safe alternative to a balloon. Anastomotic strictures presenting more than 6 months after transplant require more ERC procedures and more stents per endoscopic intervention than do strictures presenting within 6 months after transplant. Strictures that develop after 6 months also recur more often than strictures that present earlier.[18]

The treatment of an anastomotic biliary stricture is complete when there is a patent biliary anastomosis with effective biliary flow. The endoscopic endpoint for treatment can be defined as complete disappearance of the stricture by occlusion cholangiography without any significant indentation at the site of previous narrowing, as proposed by Costamagna and colleagues when they first reported the technique of multiple stent placement for benign postoperative strictures.[85] The completion of treatment also can be measured endoscopically by passing an 8.5-mm balloon through the anastomosis and subsequently visualizing biliary emptying under fluoroscopy.[14,61] Although both definitions may be somewhat subjective, clinical effectiveness can be measured definitively by the sustained resolution of cholestasis.

Repeated ERC procedures do carry some risk of complications, including cholangitis, pancreatitis, and perforation, but the complication rate of 2% to 6% is considerably lower than the risks of surgical revision or even retransplant.[53,71,89-91] When anastomotic strictures are treated by endoscopic therapy, the long-term results in terms of patient and graft survival are equivalent to those for matched controls without anastomotic strictures.[5,6,69,90]

In summary, the endoscopic management of biliary strictures can be achieved effectively and efficiently by serial ERC procedures with balloon dilation and the placement of multiple plastic stents across the strictures. Progressively larger numbers of plastic stents are placed during each successive intervention, which serves to increase the rate of sustained patency at the anastomosis and reduce the duration of treatment. ERC should be repeated at a minimum of 3-month intervals to avoid stent occlusion and secondary cholangitis, and more frequent intervention can be considered to shorten the total duration of treatment for the convenience of the patient (Figure 3).

Balloon Dilation With Metal Stent Placement There is limited experience in the use of SEMS for biliary strictures after liver transplant. A recent study showed a success rate of 70% for anastomotic strictures after DDLT treated with SEMS, and the stenting interval was only 3 to 4 months.[92] A second study compared SEMS with plastic stents for the treatment of anastomotic strictures after DDLT and reported a 100% patency rate with SEMS vs 80% with plastic stents.[93] However, a multicenter study from Europe using fully covered SEMS for the treatment of benign strictures was not so promising. In the 42 patients with strictures after liver transplant, there was a 68.3% rate of stricture resolution, and 74.7% of the stents had migrated by 6 months.[94] In general, the use of SEMS in benign strictures is limited by frequent stent migration, early occlusion, and, uncommonly, the development of new biliary strictures at the proximal aspect of the stent.[92,95,96] The problem of stent migration may be mitigated by the development of metal stents with flanges, which serve to hold the stent more securely in place within the bile ducts. Further studies will be required to establish the sustained patency and complication rates achieved with SEMS before their routine use can be recommended.

Special Situations

Living Donor Liver Transplant LDLT is associated with higher rates of biliary strictures than DDLT, with reports of strictures occurring in 13% to 36% of patients receiving living donor grafts.[9,12,21-24,97] This relatively high rate of stricture formation is attributed to the surgical techniques required to resect and salvage the right or left lobe of the liver, which can injure the bile ducts. Other factors also contribute to the higher rate of stricture formation in LDLT: the smaller diameter of the intrahepatic bile ducts (<4 mm) in the living donor graft in comparison with the diameter of the extrahepatic bile ducts in the deceased

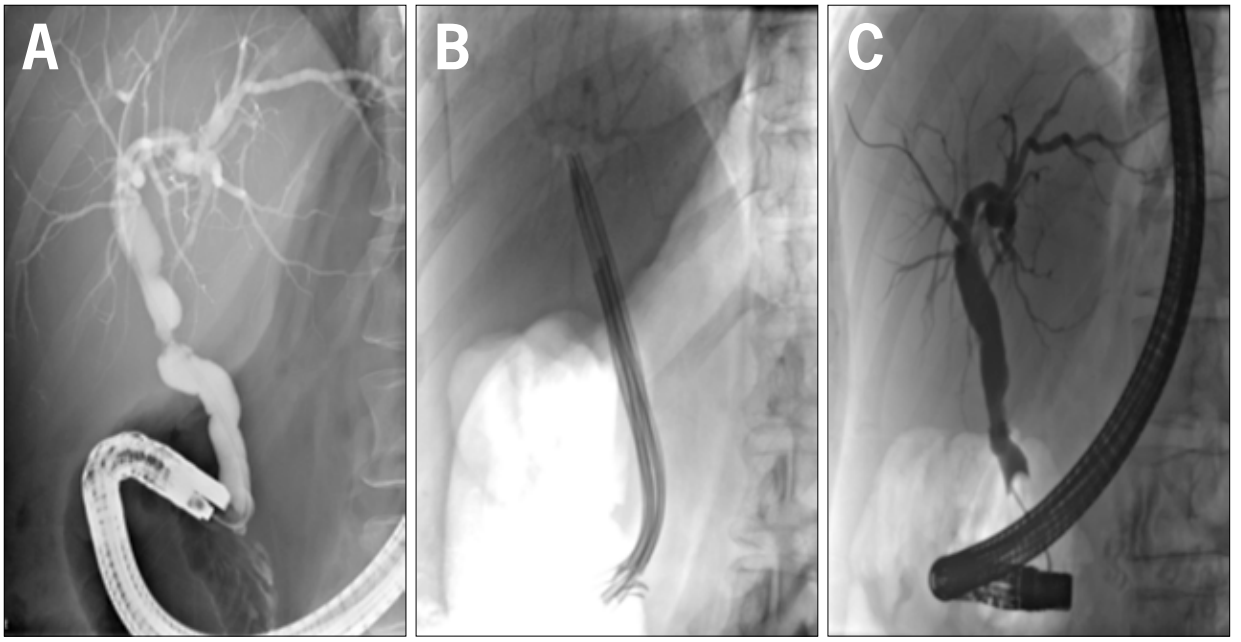

Figure 3. Cholangiograms showing an anastomotic stricture before endoscopic therapy (**A**) and with progressive stent placement to a maximum of 5 stents (**B**). Resolution of the stricture after progressive stent placement over a 9-month period (**C**).

donor graft, the frequent requirement to create multiple ductal anastomoses with the intrahepatic ducts of the living donor graft, and the higher incidence of bile leaks in the living donor graft.[2,33,98] Bile leaks are closely associated with bile duct strictures, and the high incidence of leaks may be the most important factor in stricture formation after a living donor transplant.[18,33,98] Surgical techniques continue to improve, with an associated reduction in the frequency of bile duct strictures, but there is no universally accepted approach to biliary anastomosis.[15,19,35,46,47,49,53] Duct-to-duct biliary reconstruction has a higher risk of anastomotic stricture formation than hepaticojejunostomy reconstruction in some studies, although other studies report no difference.[33,38,39]

Endoscopic therapy is the first line of treatment for anastomotic strictures after LDLT. Performing ERC with progressive balloon dilation and placing multiple plastic stents for anastomotic strictures require the same techniques developed for treating strictures after DDLT. However, the endoscopic management of strictures after LDLT can be particularly challenging because multiple biliary anastomoses can lead to multiple strictures, and the relatively small bile duct size can lead to technical difficulty in traversing a stricture and dilating it adequately to achieve sustained patency of the anastomosis. In initial reports, the endoscopic treatment of anastomotic strictures after LDLT with the standard endoscopic techniques of balloon dilation followed by stenting resulted in relatively low success rates (37%-68%) in comparison with the success rates reported in DDLT (80%-90%).[26,34,36,81-83,99,100]

However, the application of more aggressive endoscopic therapy in patients with anastomotic strictures developing after LDLT has shown promising results. In one report, balloon dilation followed by the placement of progressively greater numbers of stents for anastomotic strictures achieved sustained patency of the biliary anastomoses in 84.2% of patients (32/38) by endoscopic techniques alone.[24] The remaining 6 patients also were treated without surgical intervention but required initial treatment by PTC, which then was followed by endoscopic stenting with progressively greater numbers of stents.

In a subset of patients with LDLT, a so-called crane neck deformity can develop, in which the biliary anastomosis is located below the highest point of the recipient duct.[101] This unusual cause of biliary obstruction is thought to be related to compensatory hypertrophy of the donor lobe, which leads to sharp angulation of the bile duct.[11] It occurs in approximately 7% of anastomotic strictures, and the success rate of endoscopic therapy is approximately 20%.[101]

Nonanastomotic Strictures The etiology of nonanastomotic strictures after liver transplant is an important factor in determining whether nonsurgical therapy should be considered for a patient. Nonanastomotic strictures secondary to early hepatic artery thrombosis require urgent revascularization or retransplant for irreversible diffuse bile duct injury, whereas nonanastomotic strictures secondary to late hepatic artery thrombosis can be managed by endoscopic means. Interestingly, many patients in whom nonanastomotic strictures develop have no history

of gross arterial stenosis or thrombosis. These patients also may benefit from endoscopic therapy.

The success rates of endoscopic therapy for nonanastomotic strictures with progressive balloon dilation and plastic stents have been reported to be from 50% to 75%.[5,8,35,90] Although the results of endoscopic treatment for nonanastomotic strictures are generally favorable, they are somewhat less positive than the outcomes of endoscopic treatment for anastomotic strictures. In addition, patients with nonanastomotic strictures are more likely to require multiple interventions than those with anastomotic strictures. In 2 reports of endoscopic treatment for nonanastomotic strictures, sustained patency required a greater number of therapeutic interventions (7 vs 3), as well as a longer duration of treatment (185 vs 67 days), in comparison with endoscopic treatment for anastomotic strictures.[8,90] The treatment of nonanastomotic strictures can require persistence in all transplant recipients, and the treatment of nonanastomotic strictures after LDLT is even more challenging than treatment after DDLT. The rate of sustained patency of nonanastomotic strictures after endoscopic therapy in LDLT was 25% to 33%, compared with a rate of 50% to 75% in DDLT.[5,8,12,35,90] Ultimately, despite multiple endoscopic interventions over a prolonged interval, the ischemic and immunologic injury that leads to nonanastomotic strictures may result in continued stricture formation, so a large minority of these patients (30%-50%) will eventually require retransplant.[8,10,35] Despite endoscopic treatment, the development of nonanastomotic strictures reduces graft survival, although it does not decrease patient survival.[8,16]

Endoscopic therapy for nonanastomotic strictures should be conducted only by an experienced endoscopist and endoscopy team. For the effective treatment of strictures that are amenable to endoscopic therapy, the endoscopist must relieve obstruction resulting from secondary stones and biliary casts; overcome the technical challenges of multiple strictures, which are often in small intrahepatic ducts; and plan on performing multiple interventions over a prolonged interval.

After access to the biliary tree has been obtained, ERC-guided therapy begins with the removal of obstructing biliary sludge and casts, which may dramatically increase the length of the procedure, and then proceeds to the progressive balloon dilation and stenting of all accessible strictures. Strictures in the smaller secondary and tertiary intrahepatic bile ducts may not be amenable to endoscopic treatment, so treatment should be oriented toward improving bile outflow through the larger bile ducts rather than the elusive goal of treating all strictures.

The dilation of intrahepatic nonanastomotic strictures is guided by the size of the bile ducts. Dilation generally begins with a 4-mm balloon or over-the-wire dilator because the ducts are typically small at the first intervention, although they may enlarge over time with hepatic remodeling. Dilation at subsequent interventions can progress up to 6 mm in the right or left main intrahepatic ducts and, very occasionally, to a maximum of 8 mm for distended main intrahepatic ducts. With each endoscopic intervention, 1 or more stents are placed across the strictures to maintain their maximal diameter while healing occurs. Procedures are usually performed no less often than every 3 months to allow stent exchange before occlusion.[10] However, because of bile stasis resulting from incompletely treated strictures, biliary sludge may develop relatively quickly in patients with nonanastomotic strictures, so a 2-month interval for stent exchange may be necessary to prevent early stent occlusion and secondary cholangitis (Figure 4).

In cases where anastomotic strictures are unusually narrow, complex, or located within small intrahepatic ducts, ERC-guided therapy may fail, and PTC-guided therapy may be required for rescue therapy. With rescue PTC, the obstructed bile ducts are first decompressed to prevent acute iatrogenic cholangitis. The obstructing bile duct stricture is then crossed, balloon dilation performed, and a percutaneous stent placed across the stricture. The percutaneous stent may be placed during the first intervention, or instead a percutaneous drain attached to a biliary collection bag for external drainage may be used. When a percutaneous drain is left in place, combined PTC and ERC are undertaken at the next intervention to internalize the stent and allow conversion to a purely endoscopic approach for long-term therapy. Given the multiple interventions required to treat nonanastomotic strictures, patients prefer the endoscopic approach, which allows them to avoid the discomfort of replacing external drains and the inconvenience of managing bile collection between sessions.

Role of Cholangioscopy The routine use of intraductal cholangioscopy for the management of posttransplant strictures has not been well described. However, cholangioscopy has been found useful to provide direct visualization of passage of the guidewire across a stricture when the wire cannot traverse the stricture under fluoroscopic guidance alone.[102]

Recurrent Strictures The rate of recurrence of posttransplant biliary strictures ranges from 10% to 20%.[103] Risk factors for a decreased responsiveness to therapy include the delayed onset of strictures (strictures that present 6 months or more after liver transplant), very tight strictures, and nonanastomotic strictures.[11,18,90] The management of recurrent strictures may require more aggressive balloon dilation with the placement of additional stents or expandable metal stents to achieve a larger diameter at the anastomosis.

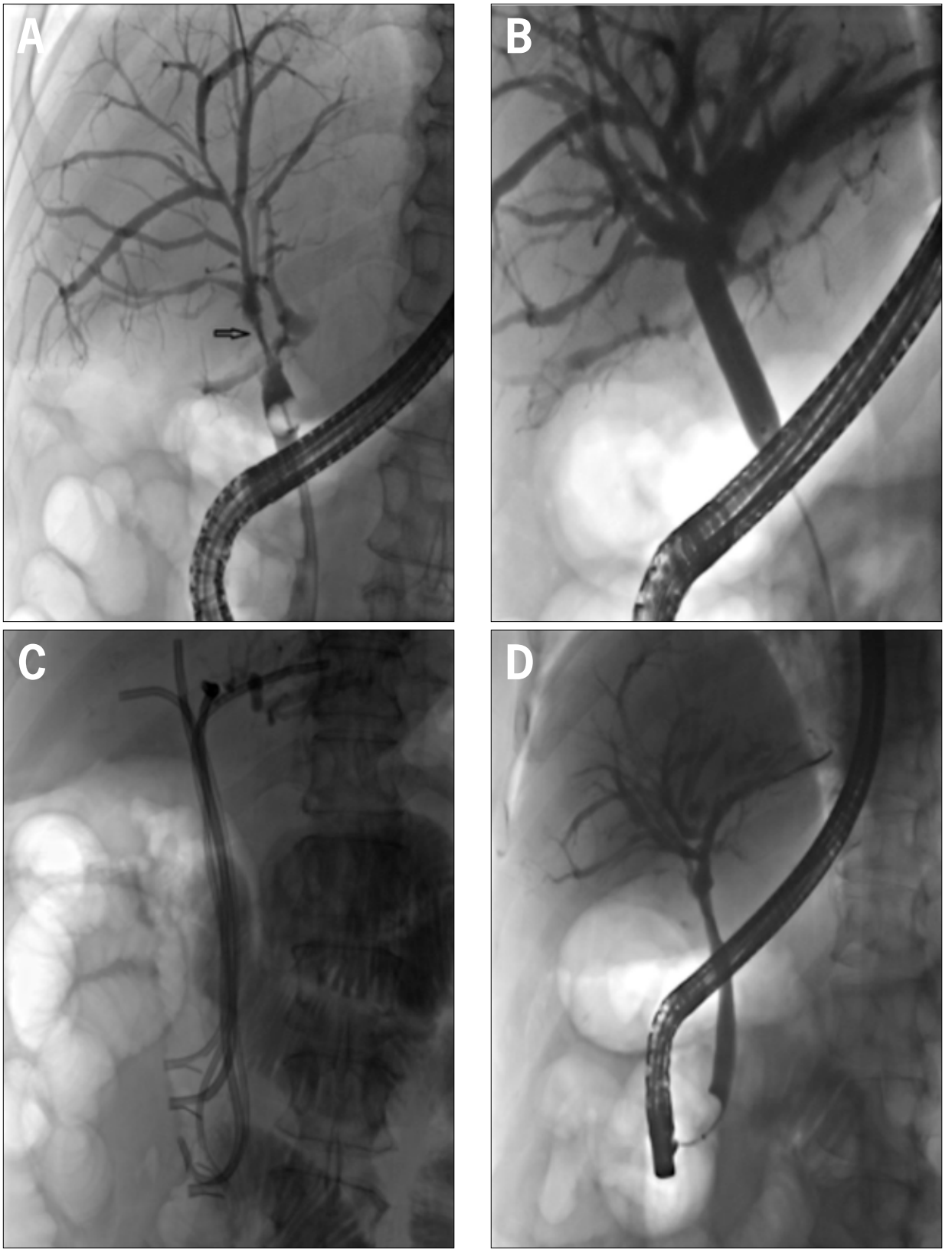

Figure 4. Cholangiograms showing a nonanastomotic stricture before endoscopic therapy (arrow, **A**), with dilation (**B**), and with progressive stent placement (**C**). Resolution of the stricture after progressive stent placement (**D**).

Percutaneous Transhepatic Cholangiography–Guided Therapy

PTC-guided therapy for biliary strictures after transplant is generally performed when ERC is not feasible, most commonly because a Roux-en-Y biliary enteric anastomosis prevents access to the biliary duct by an endoscopic approach, or when ERC has failed because of complex or tight strictures or simply because of failed biliary access. In cases in which the biliary stricture causes intrahepatic biliary dilatation, PTC usually can access the biliary tree in a safe and simple manner. In cases in which the intrahepatic ducts are not dilated, PTC is considerably more difficult. Although PTC has an overall technical success rate of 40% to 85%, it remains a second-line therapy because of its invasiveness and the potential complications of hemorrhage, bile leaks, and infection (2%-14%).[11,104-110] The risks of hemorrhage from PTC may be particularly problematic in patients with persistent thrombocytopenia or coagulopathy after transplant. Patients also find the percutaneous approach to strictures problematic because the majority of patients undergoing PTC must tolerate the presence of an external percutaneous catheter throughout a course of treatment that can extend over many months.

Surgery

Surgical revision is now reserved for patients who have strictures refractory to either ERC- or PTC-guided therapy and in whom retransplant is the last resort after all other treatment modalities have failed.[11,12,35]

When surgical revision is required for patients with a duct-to-duct anastomosis, the procedure most commonly performed is a Roux-en-Y hepaticojejunostomy. If a hepaticojejunostomy was performed initially because of primary sclerosing cholangitis or another bile duct abnormality, then an attempt is made to reposition the bile duct graft to a better vascularized area.[16]

Summary

Endoscopic therapy has revolutionized the treatment of biliary strictures after liver transplant. The endoscopic treatment of biliary strictures is effective and preserves graft function without the morbidity and mortality associated with surgical revision. The appropriate treatment of anastomotic strictures leads to favorable rates of long-term patient and graft survival that are comparable with the survival outcomes of patients in whom anastomotic strictures do not develop. Unfortunately, the same does not hold true for nonanastomotic strictures. Despite improvements in endoscopic treatment, the development of nonanastomotic strictures reduces graft survival, although it does not decrease patient survival. Repeated progressive endoscopic dilation with multiple stents is the treatment of choice for posttransplant biliary strictures. Percutaneous and surgical modalities are reserved for patients in whom endoscopic treatment fails, whether because, uncommonly, a stricture cannot be traversed with endoscopic tools or because the hepaticojejunostomy is inaccessible as a consequence of altered surgical anatomy with a long Roux-en-Y anastomosis.

The authors have no relevant conflicts of interest to disclose.

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