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Endoscopic management of biliary strictures after liver transplantation

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review focuses on the role of endoscopy in biliary strictures, one of the most common biliary complications after OLT.

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Abstract

Bile duct strictures remain a major source of morbidity after orthotopic liver transplantation (OLT). Biliary strictures are classified as anastomotic or non-anastomotic strictures according to location and are defined by distinct clinical behaviors. Anastomotic strictures are localized and short. The outcome of endoscopic treatment for anastomotic strictures is excellent. Non-anastomotic strictures often result from ischemic and immunological events, occur earlier and are usually multiple and longer. They are characterized by a far less favorable response to endoscopic management, higher recurrence rates, graft loss and need for re-transplantation. Living donor OLT patients present a unique set of challenges arising from technical factors, and stricture risk for both recipients and donors. Endoscopic treatment of living donor OLT patients is less promising. Current endoscopic strategies for biliary strictures after OLT include repeated balloon dilations and placement of multiple side-by-side plastic stents. Lifelong surveillance is required in all types of strictures. Despite improvements in incidence and long term outcomes with endoscopic management, and a reduced need for surgical treatment, the impact of strictures on patients after OLT is significant. Future considerations include new endoscopic technologies and improved stents, which could potentially allow for a decreased number of interventions, increased intervals before retreatment, and decreased reliance on percutaneous and surgical modalities. This

INTRODUCTION

Complications of the biliary tract have been considered the technical 'Achilles heel' of orthotopic liver transplantation (OLT) because of their high frequency, need for long term treatment and potential detrimental effects on graft and patient survival. While in early reports, morbidity rates of up to 50% and mortality of 25%-30% were reported, with improvements in organ selection, retrieval, preservation and standardization of the methods of biliary reconstruction, the incidence of these complications have been reduced dramatically^[1-9]. The biliary tract, however, still remains the most common site for postoperative complications in OLT^[4,10]. Biliary complications, which most frequently include bile duct strictures and leaks, also include casts, sludge, stones, sphincter of Oddi dysfunction, mucocoeles, and hemobilia in 10%-25% of cases and result in death in up to 10% of cases^[1,2,6,8,9,11-17]. These high rates of post-transplant biliary complications, may point to an inherently sensitive nature of the biliary epithelium to ischemic damage in comparison to hepatocytes and vascular endothelium^[18]. Beyond graft survival, biliary complications also have a major impact on the quality of life for an OLT recipient, as they entail frequent readmission, repeated imaging, invasive procedures, and occasional reoperation, all adding to the

significant monetary cost of OLT and to the emotional toll these patients suffer^[5]. While surgical treatment used to be the standard of care at one time, the non-operative management of biliary complications following OLT has become standard practice with primarily endoscopic techniques as the preferred diagnostic and therapeutic modalities, obviating the need for surgery in a majority of patients^[9,19,20].

This article will review the role of endoscopy in the diagnosis, treatment options, outcome, and future therapy considerations of biliary strictures after OLT, from the perspective of the practicing gastroenterologist.

INCIDENCE OF BILIARY STRICTURES

While there has been a decreasing trend in recent years, bile duct strictures are still frequent and account for approximately 40% of all biliary complications after LT, occurring with an incidence of 5%-15% after deceased donor OLT and 28%-32% after right-lobe live donor OLT, with higher incidences seen in reports with a longer follow-up^[7,14,21-33]. Strictures can occur with either type of biliary anastomosis, although according to some series, strictures were more common with Roux-en-Y hepaticojejunostomy or choledochojejunostomy reconstructions than duct-to-duct anastomoses^[1,14,21]. Although strictures can present at any time, the overwhelming majority occur within the first year after OLT^[1,23]. The mean interval at the time of presentation is 5-8 mo after OLT^[3,7,23,34,35]. Recent studies suggest that their prevalence continues to increase with time^[36]. Strictures which occur early mostly result from technical problems, whereas later strictures mainly arise from vascular insufficiency and problems with healing and fibrosis^[37,38].

CLASSIFICATION OF BILIARY STRICTURES

Biliary duct strictures can be classified according to their location; strictures localized at the site of the biliary anastomosis or anastomotic strictures are usually single while non-anastomotic strictures in other locations of the biliary tree are most often multiple^[36,39-42]. These 2 types of biliary strictures differ in incidence, etiology, presentation, natural history and response to therapy rendering their distinction clinically relevant^[25]. Biliary strictures tend to be a common problem after living donor OLT in both the donor and the recipient and are discussed separately.

Anastomotic strictures

Pathogenesis and risk factors: Anastomotic strictures occur in 5%-10% of cases, are most often isolated, short in length, and are a result of fibrotic healing within the first year after transplantation^[1,7,36]. Among the etiological factors for anastomotic strictures which appear early in the postoperative period, technical issues appear to be the most important: improper surgical techniques, small

caliber of the bile ducts, a mismatch in size between the donor and recipient bile ducts, inappropriate suture material, tension at the anastomosis, excessive use of electrocauterization for control of bile duct bleeding, and infection^[25]. Bile leak is an independent risk factor for the development of anastomotic strictures^[17]. Later onset anastomotic strictures, most likely indicate fibrotic healing arising from ischemia at the end of the donor or recipient bile duct^[34,36,38,40,43-46]. Anastomotic strictures are reported to be more common after hepaticojejunostomy than after direct duct-to-duct anastomosis^[1,14]. Duct-to-duct biliary anastomosis has the additional advantage of easy endoscopic access to the biliary system and preservation of the sphincter of Oddi which in theory avoids reflux of contents into the bile duct^[44]. While biliary complications including bile leaks and cholangitis appear to be higher in patients with T-tubes, biliary strictures appear to be increased following duct-to-duct anastomosis in non-T-tube recipients as compared to anastomosis over a T-tube^[15,47-50]. Anastomotic strictures are more frequent than non-anastomotic strictures in living donor OLT as compared to recipients of deceased donor OLT^[51-53].

Presentation: The majority of anastomotic strictures occur within the first 12 mo after OLT. Patients may be asymptomatic at presentation, with elevations of serum aminotransferases, bilirubin, alkaline phosphatase and/or gamma-glutamyl transferase levels. Occasionally, patients have non-specific symptoms such as fever and anorexia, right upper quadrant pain, pruritus, and/or jaundice. A high index of suspicion must be maintained, as pain may be absent in the transplant setting because of immunosuppression and hepatic denervation^[41,44,54].

Diagnosis: Once abnormalities in liver function chemistries raise the possibility of biliary strictures, further imaging, either noninvasive or invasive, should be performed. Biopsy may only rarely suggest the presence of pathology and thus has a limited role^[55].

Initial evaluation should include liver ultrasound (US) with Doppler evaluation of the hepatic vessels. If hepatic artery stenosis or occlusion is suspected on Doppler US, hepatic angiography is usually indicated. Unfortunately, in liver transplant patients, abdominal US may not be sufficiently sensitive (sensitivity of 38%-66%) to detect biliary obstruction^[4]. The absence of biliary dilation has been found to be an unreliable indicator of adequate biliary drainage^[49]. The size of the duct is also unreliable in following up these patients or in assessing the response to treatment. Indeed, US has been shown to have a high false negative rate in liver transplant recipients. Furthermore, there appears to be a significant lack of correlation between ductal dilation on US and the cholangiographic and clinical picture^[23,56]. It is not clear why the donor bile ducts do not respond to distal obstruction by displaying the same degree of proportional dilation as non transplanted livers, however the presence of fibrosis leading to less pliable ducts has been suggested as a possible etiology^[57]. Therefore, the absence of biliary

dilation identified on US should not preclude further evaluation with more sensitive techniques if the suspicion of biliary stricture remains strong.

Scintigraphy of the hepatobiliary tract with 99-technetium labeled iminodiacetic acid identifies strictures with 75% sensitivity and 100% specificity but a lack of therapeutic benefit limits its clinical use^[58,59]. Biliary scintigraphy is therefore rarely performed when biliary stricture is suspected but still remains an excellent test to detect biliary leaks^[58].

If there is strong clinical suspicion or an US indicates a possible bile duct obstruction, a cholangiogram should be obtained and is considered the reference standard for the diagnosis of biliary tract complications^[2,3,7,8,36,44,54]. While endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) remain the gold standard, particularly when there is a very high pretest probability of a biliary stricture and need for intervention, magnetic resonance cholangiopancreatography (MRCP) has gained increasing acceptance as a reliable technique in detecting biliary complications. In a study of 64 consecutive patients with suspected biliary complications, MRCP had a sensitivity of 95%, a positive predictive value of 98% and an overall accuracy of 95% compared to ERCP as the reference standard^[60]. MRCP is currently considered an optimal noninvasive diagnostic tool for the assessment of biliary complications after OLT^[25]. Once MRCP expertise becomes more widely available, it should have an even more prominent role in limiting the role of invasive cholangiography for therapeutic purposes. The chief disadvantage of MRCP, beyond lack of availability, is the lack of its therapeutic ability. However, it can still be used as a second step after ultrasound in patients for whom the use of ERCP or PTC carries a higher procedural risk.

Use of ERCP *vs* PTC depends on the type of biliary reconstruction, the likelihood of therapeutic intervention and the available expertise. ERCP has the advantage over PTC as it is not only more physiological but also less invasive. In most large tertiary care centers, ERCP is seen as the best diagnostic and therapeutic intervention in patients with duct-to-duct anastomosis. PTC is most often reserved for patients in whom ERCP is unsuccessful and in patients with Roux-en-Y hepaticojejunostomy or choledochojejunostomy. While an inherent limitation of ERCP is the problem of access in patients with Roux-en-Y reconstructions, in high volume centers with experienced endoscopists, newer approaches of ERCP can be successfully performed using the variable stiffness colonoscope, double balloon enteroscope, single balloon enteroscope, and spiral overtube^[61-64].

The characteristic cholangiographic appearance of an anastomotic stricture is that of a thin, short, localized, isolated narrowing in the area of the biliary anastomosis. In some patients, a transient narrowing of the anastomosis may become evident within the first 1-2 mo after OLT as a result of postoperative edema and inflammation^[36].

Management: Over the past 2 decades, there has been

a transition in the primary management of anastomotic strictures from predominantly surgical management to primarily endoscopic management. Percutaneous therapy, although it has a success rate of 40%-85% is still considered a second-line option because of its invasive nature and the associated complications of hemorrhage, bile leaks and significant morbidity^[5]. Surgical revision is now reserved for patients who have failed the endoscopic and transhepatic measures, and retransplantation is the final option when all else fails^[1,21,23,65].

Balloon dilation alone without stent placement is only successful in approximately 40% of cases^[66]. Balloon dilation with additional stent placement however, appears to be more successful with a durable outcome in 75% of patients with anastomotic strictures^[32,66]. Placement of not one, but multiple side-by-side plastic stents further increases successful outcomes in 80%-90% of patients^[67-69]. There is some experience in temporary placement of covered self-expanding metal stents to reduce the need for repeated stent exchanges, but the data are limited^[70]. A smaller subset of patients, with transient narrowing of the anastomosis within the first 1-2 mo after OLT, presumably due to postoperative edema and inflammation, may respond with a single intervention of endoscopic balloon dilatation and plastic stent placement without need for further treatment^[36].

Most patients with anastomotic strictures require ongoing ERCP sessions every 3 mo with balloon dilation of 6-10 mm and multiple stents of 7 Fr to 10 Fr repeated for 12-24 mo^[54,68,69]. Stents are exchanged at 3-monthly intervals to avoid stent occlusion and bacterial cholangitis. An increasing number of stents can be used at each session to achieve a maximum diameter. The majority of patients require several endoscopic interventions, with a mean of 3 to 5 with long term success rates in the range of 70%-100%^[3,32,36,37,68,69,71-74]. A protocol of accelerated dilation every 2 wk, and a shortened stenting period of an average of 3.6 mo, showed some encouraging results with a high 87% success rate^[68]. In patients with duct-to-duct anastomosis, endoscopic management is hence first line, and it appears that while repeat endoscopic treatment is needed, shorter intervals in between treatments may ultimately reduce the time needed for successful long term outcomes (Figure 1).

The major drawbacks of endoscopic dilation with placement of one or more stents as a standard of care in the management of anastomotic strictures, are the need for multiple procedures repeated over extended periods of time, and the risk of cholangitis resulting from stent occlusion.

When endoscopic access to the anastomotic stricture is unobtainable, as in Roux-en-Y reconstructions, another option to be considered is a combined approach where access to the biliary tree is obtained *via* a percutaneous transhepatic route followed by "rendezvous" endoscopy^[62,75]. Management including using percutaneous transhepatic drainage achieves success rates of 50%-70%^[74]. The role of surgical revision is confined to endoscopic failures, and the long term results are good with no effect on patient or graft survival^[7,11,76].



Figure 1 Cholangiograms showing anastomotic stricture (A) dilated and stented with 3 plastic stents (B) leading to resolution of the stricture (C).

Natural history: Patients with anastomotic strictures require long term surveillance since strictures often recur. Anastomotic strictures identified within 6 mo after OLT usually have a good response to short term stenting (3-6 mo), with the lowest recurrence rates^[36]. Anastomotic stricture recurrence, however, is particularly high among patients with an initial delayed presentation beyond 6 mo after OLT, and very tight strictures^[5]. Surveillance is lifelong in all anastomotic stricture patients with a need for periodic evaluation of liver enzymes and imaging. In an illustrative study, patients who developed biliary strictures after OLT and were initially treated endoscopically with balloon dilation and plastic stents, had a recurrence rate of 18% with a mean time to recurrence of 110 d^[71]. However, patients appear to respond well to repeated endoscopic treatment after recurrence^[68]. Overall, when anastomotic strictures are treated appropriately, the long term results in terms of patient and graft survival are equivalent to those for matched controls without anastomotic strictures^[2,3,77].

Non-anastomotic strictures

Pathogenesis and risk factors: Non-anastomotic strictures account for 10%-25% of all stricture complications after OLT, with an incidence of 1%-19%; these are often multiple, longer and occur earlier than anastomotic strictures. Multiple factors contribute to the occurrence of non-anastomotic strictures with the main categories of risk factors including ischemia-related injury with or without hepatic artery thrombosis, immunologically-induced injury including chronic ductopenic rejection, and cytotoxic injury induced by bile salts^[1,23,25,29,35,39,77]. Ischemic and immunological injuries to the biliary epithelium are the most important contributors. Ischemic injury may result from arterial insufficiency and hepatic artery thrombosis, or other forms of ischemia because of donation after cardiac death, prolonged use of vasopressors in donors, older donor age or longer cold and warm ischemia times^[1,3,26,27,78-85]. Immunological injury is assumed to be a risk factor based on the relationship of non-anastomotic strictures with ABO incompatibility, polymorphism in genes encoding chemokines, and pre-existing immunologically-mediated disease seen in recipients with underlying disease such as primary sclerosing cholangitis (PSC) or autoimmune hepatitis^[78]. Less important and

inconsistent are the reported associations with hepatitis C and cytomegalovirus^[21,39,86].

Presentation: Non-anastomotic strictures tend to occur earlier than anastomotic strictures, with a mean time to stricture development of 3-6 mo^[23,39]. Buis *et al*^[78] further reported that non-anastomotic strictures secondary to ischemic causes presented within 1 year of transplant, whereas the occurrence after 1 year was more often related to immunological causes as the risk factors. Patients appear to present with similar non-specific symptoms as patients with anastomotic strictures^[42].

Diagnosis: Diagnosis of non-anastomotic strictures is made with the same modalities as those described for anastomotic strictures. Non-anastomotic strictures can occur proximal to the anastomosis in the extra- or intra-hepatic bile ducts. These strictures tend to be multiple, and longer in length^[23,29,39]. There may be multiple strictures involving the hilum and intrahepatic ducts causing a cholangiographic appearance that resembles PSC. Biliary sludge can accumulate proximal to the strictures leading to the formation of casts^[42]. Biliary sludge and casts can rapidly accumulate even after the biliary tree has been cleared and adequate drainage has been achieved. This most likely arises from ongoing sloughing of the biliary epithelium as a result of the underlying ischemic or immunologic injury^[5].

Management: Non-anastomotic strictures are more difficult to treat than anastomotic strictures with more complications of cholangitis, and overall less favorable outcomes including increased graft loss and death. Only 50%-75% of patients have a long term response to endoscopic therapy with dilatation and stent placement compared to 70%-100% in patients with anastomotic strictures as described above^[2,3,23,54,77]. Accumulation of biliary sludge and casts renders therapy particularly difficult because of rapid stent occlusion. Non-anastomotic strictures require an increased number of interventions compared to patients with anastomotic strictures^[23]. Time to response with non-anastomotic strictures is more prolonged than with anastomotic strictures^[23]. In an illustrative study, the median time of response was 185 d for non-anastomotic strictures *vs* 67 d for anastomotic strictures^[77]. Also, treatment of non-anastomotic

strictures did not result in significant long term improvement of liver chemistry^[23]. It does not appear that the poor response of non-anastomotic treatment to treatment varies with etiology^[39].

Endoscopic therapy of non-anastomotic strictures typically consists of extraction of the biliary sludge and casts which are routinely present, and balloon dilation of all accessible strictures followed by placement of plastic stents with replacement every 3 mo^[39]. Balloon dilation of all strictures is frequently not feasible because of the multifocal distribution of the strictures and their predilection for the smaller intrahepatic ducts. Furthermore, rapid stent occlusion with recurrent cholangitis is an ongoing challenge when managing non-anastomotic strictures. Finally, ischemic events which are associated with diffuse intrahepatic bile duct strictures are associated with poor graft survival, and in most instances may require early retransplantation in suitable cases. Hence, endoscopic therapy is also first line in non-anastomotic strictures and may occasionally be a definite solution, but appears to play a more prominent role as a bridge to liver retransplantation^[46,85].

Natural history: Patients with non-anastomotic strictures require lifelong surveillance since strictures are likely to recur. Complications with cholangitis after treatment are not uncommon, with subsequent repeated need for hospitalization. Most importantly, non-anastomotic strictures may result in significantly increased graft loss; up to 30%-50% of patients undergo retransplantation or die as a consequence of this complication despite endoscopic therapy^[23,39,44,54,87].

Surgical revision may ultimately be required in patients with strictures that are refractory to endoscopic or percutaneous treatment. A Roux-en-Y hepaticojejunostomy is usually performed in patients with duct-to-duct anastomosis. In those who already have a Roux-en-Y hepaticojejunostomy anastomosis, a revision may be required by repositioning the bile duct of the graft to a better vascularized area^[42].

Living donor liver transplantation associated biliary strictures

Biliary complications are more common in living donor OLT patients compared to deceased donor OLT patients, occurring in up to 32% of patients compared to 10%-15% of patients who undergo deceased donor OLT^[51,88]. Studies have shown that despite the difference in incidence, the types of complications are similar with biliary strictures as the most common^[54]. Living donor OLT patients present a unique problem, as not only are recipients at increased risk of biliary duct strictures, but donors too are at risk of these complications. Living donor OLT patients present with the usual factors putting them at risk of biliary strictures, but also with factors unique to surgical techniques required for living donor OLT. The presence of bile leaks has emerged as one of the most important factors in the causation of these strictures, in addition to elderly donors and small duct size (< 4 mm) in duct-to-duct anastomoses^[22,42,66,87,88]. It appears

that rates of complications with bile duct strictures after Roux-en-Y reconstructions and duct-to-duct anastomoses are similar^[22]. Presentation is not unlike that in deceased donor OLT patients, however a recent report highlighted the use of a serum bilirubin over 1.5 mg/dL as a better indirect marker of biliary stasis in these patients than alkaline phosphatase which may be overly sensitive^[89].

Recipient-associated biliary strictures: Bile duct strictures occur in an estimated 1%-9% of these patients^[88,90]. Ischemic biliary injury in recipients of living donor OLT is a well recognized risk factor which has been associated with extensive dissection of the right hepatic artery and bile duct in the donor in early cases of living donor OLT. In living donor transplantation the incidence of anastomotic strictures appears to be consistently higher than non-anastomotic strictures as compared with recipients of whole liver grafts^[51-53]. This is considered to be related to the blood supply of the anastomosis and often the presence of multiple and small caliber donor ducts. In terms of management, the therapeutic value of ERCP and PTC in living donor OLT is still under evaluation^[5,54]. Methods of treatment and success rates of long term endoscopic intervention therapy are difficult to interpret because of the presence of multiple ductal anastomoses, smaller size, peripheral location and increase risk for devascularization^[51-53]. To date, only 6 published trials have evaluated the efficacy of endoscopic therapy in anastomotic strictures after living donor OLT^[24,30,35,52,84,87,91]. Endoscopic treatment success rates appear significantly less than for anastomotic strictures in deceased donor OLT at 60%-75%^[52,84,87,91]. Just as in deceased donor OLT patients, the combination of balloon dilation and stenting is more effective than either modality alone^[91]. Technically, living donor OLT presents a challenge with the most common reason for failure being the inability to traverse the stricture and complex peripheral anastomosis, rendering plastic stent placement difficult^[52]. A subset of patients with a sharp angulation or "crane neck" deformity of the bile duct may make strictures resistant to endoscopic treatment^[53]. Percutaneous transhepatic therapy appears safe and effective when ERCP fails^[53,92,93]. Non-anastomotic strictures in living donor OLT have even lower success rates ranging from 25% to 33%, significantly below the 50%-75% seen in patients with deceased donor OLT^[31,52,53,92,93]. Overall, surgical revision is carried out more frequently in recipients after living donor OLT than after deceased donor OLT^[87].

Donor associated biliary strictures: In living donor OLT, not only recipients but also donors are at risk of biliary complications including biliary duct strictures. While the overall incidence of bile duct injury in liver donors is low, biliary strictures are increasingly recognized complications in this subset of patients and have even been reported much beyond the early postoperative period^[94-97]. In a survey of 1508 donors in Asia, complications were seen more commonly with right-lobe as compared to left-lobe or left lateral segment donation^[90].

The general principles of management discussed earlier for all biliary strictures apply to living donors with biliary strictures. Similar outcomes were noted for both donors and recipients with biliary strictures with surgical revisions needed more often than for deceased donor OLT^[87].

FUTURE DIRECTIONS

Innovations in ERCP techniques are likely to change the management of biliary duct strictures in the future. Technical reasons for failure of therapeutic ERCP indicate that the presence of a stricture that is too tight to allow access to the central duct system is the most common cause of ERCP failure in anastomotic strictures, non-anastomotic strictures and biliary strictures after living donor OLT^[36,42]. Use of new intraductal endoscopy technologies such as the SpyGlass direct visualization system (Boston Scientific, Natick, Mass.), which allows visualization of the inner wall of the biliary tree and can act as the guidance system for passage of the guidewire through a tight stricture, has shown some early promise in this area^[5,98-100]. A recent case report detailed the use of methylene blue-aided chromoendoscopy *via* peroral cholangioscopy to successfully optically diagnose extensive ischemic-type non-anastomotic biliary lesions after transplant^[101]. Also, new types of balloons and stents will also have a significant role in improvement of management of biliary strictures. Preliminary evidence shows that peripheral cutting balloons may be more effective in biliary strictures not responsive to standard measures^[102]. Plastic stents and catheters presently used carry a high risk for occlusions. Use of larger metallic open mesh or partially covered stents increases the probability of patency but carries several disadvantages including ingrowths of tissue from reactive hyperplasia, their permanency and the potential difficulty of removing them at surgery. Therefore uncovered and partially covered self-expandable metal stents cannot be recommended for therapy of biliary strictures. Newer removable fully covered metal stents could offer potential therapeutic options for patients with biliary strictures with increased duration of patency than plastic stents^[25]. More distant in the future are bioabsorbable stents which could be deployed and would remain in place for several months with subsequent biodegradation. These innovations will hopefully allow treatments with single interventions rather than the current practice of repeated interventions and thus have a significant positive impact on the quality of life of the patients treated.

CONCLUSION

Despite advances in organ procurement and surgical techniques, biliary complications remain a significant source of morbidity in patients after OLT, with biliary strictures still among the most common of these complications. In recent years, endoscopy has played a progressively greater role in the diagnosis and

management of biliary stricture complications after transplantation. Repeated endoscopic dilation with placement of one or more plastic stents is currently the standard first line management of biliary strictures avoiding the need, particularly in anastomotic strictures, for percutaneous transhepatic approaches and surgical management in most cases. Percutaneous and surgical modalities are now reserved for patients in whom endoscopic treatment fails and for those with multiple inaccessible intrahepatic strictures or Roux-en-Y anastomoses. Even in these latter cases, with the recent advances of deep small bowel enteroscopy techniques, the role of endoscopic therapy is expanding. Indeed, as technology progresses with newer endoscopic techniques including intraductal endoscopy, this will allow for enhanced access and visualization of complex strictures as well as improved stenting modalities, and offer hope that the burden to OLT patients related to biliary stricture complications will be reduced even further in the future.

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