TOPIC HIGHLIGHT

2016 Liver Transplantation: Global view

Advances in endoscopic management of biliary complications after living donor liver transplantation: Comprehensive review of the literature

Milljae Shin, Jae-Won Joh

Milljae Shin, Department of Surgery, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul 143-729, South Korea

Jae-Won Joh, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 135-710, South Korea

Abstract

Apart from noticeable improvements in surgical techniques and immunosuppressive agents, biliary complications remain the major causes of morbidity and mortality after living donor liver transplantation (LDLT). Bile leakage and stricture are the predominant complications. The reported incidence of biliary complications is 15%-40%, and these are known to occur more frequently in living donors than in deceased donors. Despite the absence of a confirmed therapeutic algorithm, many approaches have been used for treatment, including surgical, endoscopic, and percutaneous transhepatic techniques. In recent years, nonsurgical approaches have largely replaced reoperation. Among these, the endoscopic approach is currently the preferred initial treatment for patients who undergo duct-to-duct biliary reconstruction. Previously, endoscopic management was achieved most optimally through balloon dilatation and single or multiple stents placement. Recently, there have been significant developments in endoscopic devices, such as novel biliary stents, as well as advances in endoscopic technologies, including deep enteroscopy, the rendezvous technique, magnetic compression anastomosis, and direct cholangioscopy. These developments have resulted in almost all patients being managed by the endoscopic approach. Multiple recent publications suggest superior long-term results, with overall success rates ranging from 58% to 75%. This article summarizes the advances in endoscopic management of patients with biliary complications after LDLT.

Key words: Biliary complication; Endoscopic retrograde cholangiography; Endoscopic management; Living donor; Liver transplantation

Core tip: Living donor liver transplantation (LDLT) has become an accepted therapeutic option for patients with end-stage liver disease. However, biliary complications remain the major causes of morbidity and mortality for LDLT recipients and donors. Although there are currently no reports of a clear therapeutic algorithm, many approaches have been developed to treat biliary complications, including surgical, endoscopic, and percutaneous transhepatic techniques. Endoscopic treatment is currently the preferred initial treatment for patients that have previously undergone duct-to-duct biliary reconstruction. This article discusses various aspects of endoscopic management of biliary complications that occur in LDLT.

INTRODUCTION

Because of the shortage of deceased donor organs, living donor liver transplantation (LDLT) has emerged as a widely accepted therapeutic option for patients with end-stage liver disease. There have been noticeable improvements in the surgical techniques, graft preservation technology, and immunosuppressive therapies for this procedure. However, biliary complications remain the major cause of patient morbidity, graft loss, and mortality following LDLT[1-6]. Although the overall incidence of biliary complications in LDLT recipients has gradually declined leading to a considerable drop since 2008[6], many investigators have reported recently that approximately 15%-40% of adult recipients will develop biliary complications after LDLT, with considerable variation among transplant centers[5,7-13].

Spectrum of biliary complications in LDLT

Biliary complications from an LDLT procedure include biliary stricture, bile leakage, biloma, bile duct obstruction (with stones, sludge, or casts), sphincter of Oddi dysfunction, hemobilia, and mucocele[14-16]. Among these, bile leakage and anastomotic stricture are the predominant complications[7,17,18]. Patients often develop more than one complication[16,19].

Biliary strictures have been reported to develop in 18%-32% of LDLT patients regardless of the graft type[2,8,9,20-26]. Although a stricture can present at any time after transplantation, the median time interval between LDLT and the onset of biliary stricture was 5.9 mo[27]. Approximately 70%-87% of biliary strictures occur within one year of LDLT[28]. Biliary strictures are classified according to their location into anastomotic or non-anastomotic[29]. Anastomotic stricture is single and is caused by localized fibrosis due to the operative technique, postoperative bile leakage, or peribiliary ischemia[14]. Posttransplant biliary stricture occurs primarily at the anastomotic site, and it is the most common surgical complication of LDLT[12,19,21,30]. In contrast, non-anastomotic strictures are usually multiple and more diffuse, involving the hilum and intrahepatic bile duct[14,19,31]. They are thought to be the result of ischemic-, immunologic-, and bile salt-induced cytotoxic injuries[14,32,33]. With the benefit of the short ischemic time and the donor being immunogenetically healthy, there are very few reports of non-anastomotic strictures after LDLT[33].

Bile leakage can originate from the anastomotic site, remnant cystic duct stump, T-tube tract, cut surface of the graft, or a damaged accessory bile duct[14,19,31]. Similar to strictures, anastomotic leakage often results from vascular insufficiency or ischemic injury[19]. The incidence of bile leakage after LDLT ranges between 5% and 18%[9,21,22,25,28]. In one series, bile leakage comprised 65% of the LDLT patients with posttransplant biliary complications[13]. Bile leakage is a complication that predominates in the early period after LDLT, and in 70% of cases it is found within the first month after LDLT[30]. The median time interval between LDLT and bile leak was 0.7 mo[27]. Bile leakage can be classified as early or late. Early leakage is usually detected at the anastomotic site and is often related to technical problems. Late leakage, although an infrequent event, is typically associated with the removal of the T-tube[14,19,31] and may be accompanied by severe stricture due to a chronic inflammatory reaction[34]. As the bile leakage grows, extravasation of bile can result in a biloma, as a form of intrahepatic bile lake, extrahepatic bile collection, and abscess. Most bilomas encountered after LDLT are in the perihepatic space[19]. It is usually associated with a disconnected or strictured bile duct[14,31].

Bile duct stones, sludge, and casts, together called bile duct filling defects, occur in approximately 5% of patients after LDLT[12,29,31,33]. The majority of such defects are caused by stones[19]. Bile duct stones appear a median of 19 mo after LDLT[27], and casts present within the first year after transplantation, usually within 16 wk[35]. Theoretically, any condition that can obstruct bile flow can predispose to stones, sludge, and casts[14,33]. These filling defects are seen in strong association with ischemic events and are often accompanied by other biliary complications, most commonly biliary stricture[19,35-37]. In general, patients with persistent biliary stricture due to an ischemic etiology often manifest with recurrent intrahepatic biliary stones and sludge. Stones and sludge repeatedly accumulate proximal to the stricture, which leads to the formation of casts and a high incidence of cholangitis[38].
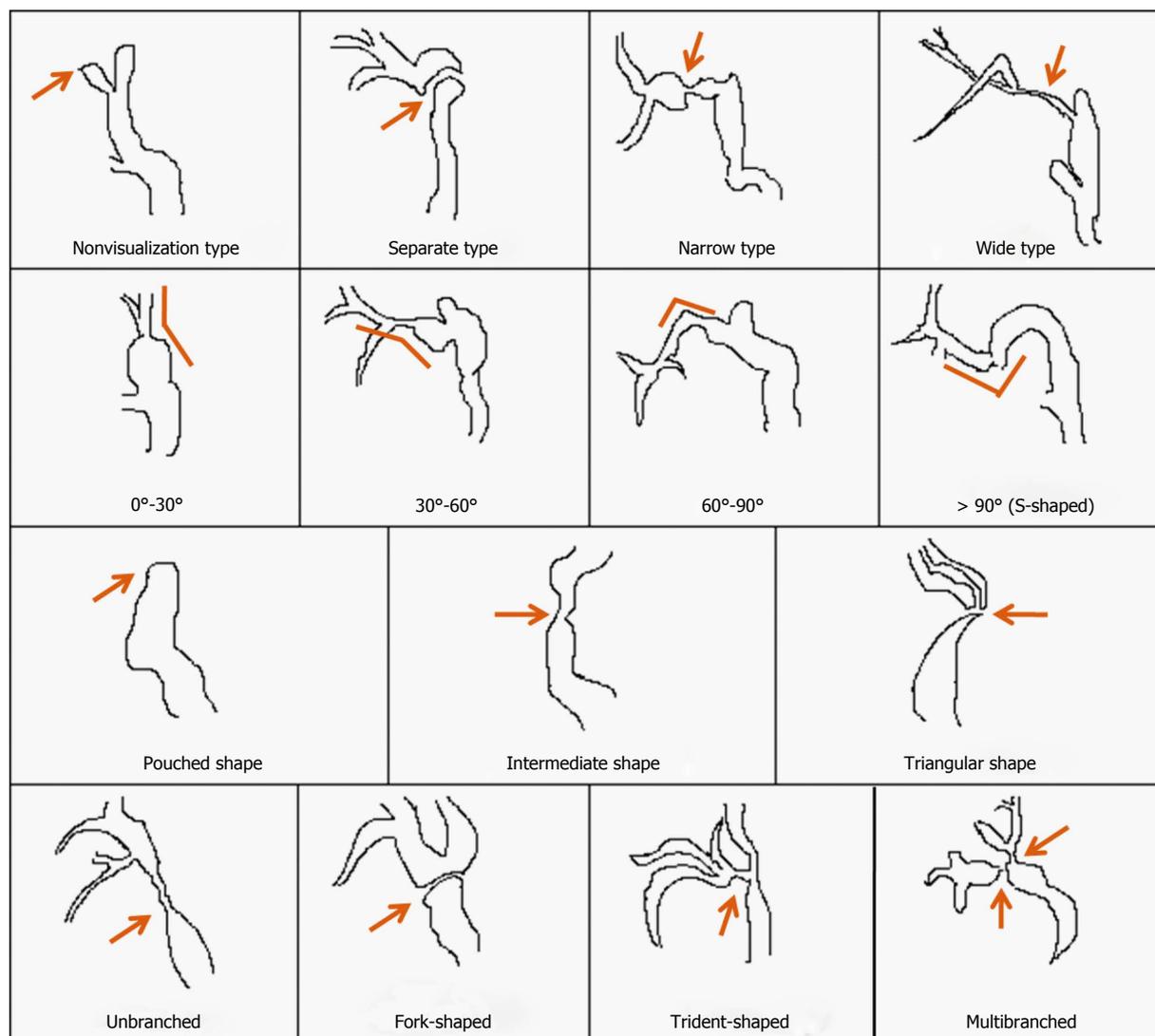
Figure 1 Example of biliary anastomotic stricture after adult living donor liver transplantation.

Types of biliary anastomotic strictures

Several reports have proposed various classifications for dividing the types of biliary anastomotic strictures that occur after an LDLT (Figure 1)[39]. There is a general consensus that the clinical outcomes and prognoses of the different types of strictures are markedly distinct. As described later, the feasibility and success rate of endoscopic intervention are heavily dependent on the categories of strictures defined on the basis of cholangiography. These may reflect the severity of stricture[37]. In a recently published study, biliary anastomotic strictures were classified by the morphology of stricture and were divided into the nonvisualization, separate duct, narrow stricture, and wide stricture types[23]. They also classified the strictures by the angle between the proximal and distal ducts: 0°-30°, 30°-60°, 60°-90°, and > 90° (S-shaped stricture)[23].

In comparison, some studies divided strictures into three types (pouched, intermediate, or triangular),

based on the shape of the distal-side (donor) of the bile duct anastomosis[37,40]. One found that initial bile leakage had an important role in the formation of pouched strictures[37]. Occasionally, the pouched type is named round type, and the triangular type is named tapered type[23]. Additionally, several Japanese groups divided strictures into four types based on the number of biliary strictures at the proximal side of the biliary anastomosis: unbranched, fork-shaped, trident-shaped, and multibranched (more than three strictures)[12,25,41]. Interestingly, in right lobe LDLT, most of the biliary anastomotic strictures were fork-shaped or trident-shaped strictures, even if the biliary system had been reconstructed in a single duct-to-duct anastomosis[12,41]. They proposed that this finding suggested that these biliary strictures arose as a result of ischemic changes extending from the anastomotic site to the proximal biliary tree of the graft[41]. One study observed a progression of strictures from mild to severe during the period of endoscopic treatment[22].

Risk factors for biliary complication

Several factors have been identified that can lead to biliary complications after LDLT[37,38,42]. Ischemic damage, such as hepatic artery compromise, is thought to be the most important factor[31,41,43]. Further potential ischemic damage is associated with the impairment of peribiliary vascular plexus as a result of prolonged ischemic time or ischemia-reperfusion injury during LDLT. The bile duct epithelium is more vulnerable to anoxic reoxygenation injury than are hepatocytes and the vascular endothelium[44]. An increased incidence of biliary complications is also associated with technical factors during surgery, which include excessive dissection of periductal tissue, electrocauterization for duct stump bleeding, and tension of the duct anastomosis[30,31]. Additionally, an organ from an elderly donor[5], Model for End-stage Liver Disease score greater than 35[45], routine T-tube placement[19,31], urgency of transplantation[24], and immunologic factors such as ABO blood type incompatibility, repeated rejection episodes and chronic rejection[46] were recognized as risk factors for biliary complications. Some recent studies found a history of bile leakage in the postoperative period to be a significant predisposing factor for stricture development[5,22,24,43].

Whether the rate of biliary complications is lower in patients undergoing a duct-to-duct choledocho-choledochostomy than in those undergoing a Roux-en-Y choledocojejunostomy has been controversial[21,47-49]. However, currently it is generally agreed that the type of biliary reconstruction does not affect the development of biliary complication after LDLT[8,31,50]. The duct-to-duct anastomosis is usually preferred for adult LDLT recipients because it provides the advantages of a shorter operation time, more physiologic bilioenteric continuity, easy endoscopic access to the biliary system, and preservation of the sphincter of Oddi, which avoids reflux of intestinal contents into the bile duct and reduces the risk of cholangitis[2,5,11,21,37,42,51].

LDLT as a risk factor for biliary complication

Biliary complications are more frequent with transplants from living donors compared with transplants from deceased donors[18,19,52,53], and these complications occur with a higher frequency in right liver grafts than in left liver grafts[21]. Increased incidences of biliary complications after LDLT are associated with small diameter and short stump of the anastomotic bile duct, biliary anatomical diversity, complex surgical procedures, occasionally creation of multiple bile duct anastomoses, local ischemia of the peribiliary plexus, and angulated duct anastomosis caused by hypertrophy of the liver graft[5,8,12,30,42,54,55]. Furthermore, a discrepancy in luminal diameter between the donor and recipient bile duct[15,56] and the presence of more than one duct orifice in the graft[8,43,57,58] are significant contributing factors for the development of biliary complications. Because of these variable difficulties, the process of LDLT itself serves as a risk factor for biliary complications[4,14,31].

Treatment options for biliary complication

Posttransplant biliary complications occasionally lead to recurring hospital admissions or to graft failure, which necessitates re-transplantation, both of which increase the costs of treatment[7,15,19,59]. Therefore, early diagnosis and prompt, adequate management of biliary complications have a significant role in determining the recipient's quality of life as well as graft survival[15,19]. Although no clear therapeutic algorithm has yet been established, many modalities to treat biliary complications have been developed, including endoscopic techniques, percutaneous transhepatic intervention, and surgical procedures[14,46,48]. The traditional primary approach to management of these conditions in the past was predominantly surgical[27]. However, with growing expertise, physiologic loads on patients and complication rates related to nonsurgical procedures are acceptably low in comparison with surgical procedures[11,30,43,60]. At present, nonsurgical approaches have largely replaced reoperation as the initial treatment of biliary complications[7,11,24,30]. In particular, great developments in endoscopic techniques over the past decade have allowed successful endoscopic access, with demonstrated efficiency in the treatment of the majority of biliary complications[5,11,12,22,26,46]. Endoscopic treatment is now considered to be the preferred first-line modality for patients that have previously undergone duct-to-duct biliary reconstruction, as it is less invasive, safe, effective, more easily accessible, and more convenient for the patient[3,5,9,12,23,25,35,38,47,61,62]. Percutaneous transhepatic therapy is then subsequently considered in cases where the endoscopic approach has failed[3,62]. Surgical revision or conversion from duct-to-duct to Roux-en-Y hepaticojejunostomy anastomosis is very complicated and technically demanding, and is therefore reserved as a rescue therapy when all other modalities have proven unsuccessful[6,14,15,29].

Endoscopic procedures have proven effective and beneficial in the management of biliary complications after deceased donor liver transplantation (DDLT)[63-65]. However, it remains controversial whether to apply the same endoscopic procedures to LDLT cases, because LDLT differs from DDLT in the type of graft used[59]. According to a recent report from the Adult-to-Adult Living Donor Liver Transplantation Cohort Study consortium (A2ALL), although the incidence of biliary complications after LDLT is higher than after DDLT, treatment requirements and time to resolution after development of a biliary complication are similar in LDLT and DDLT recipients. These data refute the common impression that biliary complications after LDLT are a more protracted and less resolvable problem than those occurring after DDLT[13]. Endoscopic treatment of biliary

complications is equally efficacious in both LDLT and DDLT recipients and should continue to be the first-line of therapy[35].

Purpose

In this review article, we describe various aspects of endoscopic management of biliary complications after LDLT, including an extensive review of the current literature.

GENERAL PRACTICE OF ENDOSCOPIC MANAGEMENT

An endoscopic technique with endoscopic retrograde cholangiography (ERC) is the primary approach for diagnosing and treating biliary complications after LDLT with duct-to-duct biliary reconstruction. After an overnight fast and conscious sedation, the procedure is performed using a video duodenoscope. The bile duct is selectively cannulated, and a contrast agent is injected through the catheter into the biliary system to obtain a fluoroscopic image. After identification of the type, site, and shape of the biliary complication, based on the completed cholangio-graphic findings, appropriate therapeutic interventions are performed[12,18,24,28,37,40,56,59,66]. Conventional the-rapeutic endoscopy universally involves endoscopic sphincterotomy and cross with a variety of guide-wires, measuring 0.018, 0.025, or 0.035 inches in diameter, through the corresponding lesion, for secure and easy repeated access[22]. The details of the therapeutic interventions follow below.

Biliary stricture: Anastomotic stricture

If there is an anastomotic stricture, once a guide-wire is traversed into the bile duct proximal to the stricture site, balloon dilatation and endoscopic retrograde biliary drainage (ERBD) stent placement is the current standard treatment[14,15,22,23,36,47,67,68]. This approach has been demonstrated to be more effective compared with balloon dilation alone[27,29,63,69]. The balloon is gradually inflated as large as the donor duct size, and single or multiple plastic stents are subsequently inserted. The procedure must be repeated every 3 mo to evaluate the progression of complicated lesions, to dilate the stricture site, to minimize stent occlusion, and to prevent cholangitis or stone formation[29,47,69]. In addition, an increasing number and larger diameter of stents are progressively replaced at each sequential ERC session to achieve a maximum diameter and greater dilatation[14,15,36]. There are various protocols for applying this routine technique. A few groups carry out balloon dilatation alone at the first ERC, and if there is residual stricture on follow-up ERC, placing ERBD stents across each stricture[12]. Recently, more aggressive approaches using maximal balloon dilation and multiple parallel stents, up to the maximum number allowed by the bile duct diameter, with an additional stent placed adjacent to the first stent, reportedly achieved more expeditious resolution of anastomotic strictures[70-72]. Some studies suggest trying to insert as many stents as possible at the first ERC[24,28]. One study suggests rapid-sequence ERC with accelerated dilatation every 2 wk and a shorter stenting duration of an average of 3.6 mo[72]. In addition, before 4 wk posttransplant, a stent is placed without balloon dilation to avoid anastomotic disruption[47]. The total duration of stent deployment averages from 6 to 12 mo, with an average of 3 to 4 stent exchange sessions[19,36,56,63,73]. The treatment in most patients with anastomotic stricture requires balloon dilation of 4 to 10 mm for 30 to 60 s and an ERBD stent of 7 to 10 Fr[15,19,40,63,72].

Biliary stricture: Non-anastomotic (hilar and intrahepatic) stricture

Endoscopic management is also the first-line modality for non-anastomotic strictures, which is similar to the approach for anastomotic strictures. It includes balloon dilatation of accessible strictures, ERBD stent placement at multiple lesions, and exchange every 3 mo[14,19,31,32,38,74]. However, the endoscopic treatment of non-anastomotic stricture is more difficult and less satisfactory than that of anastomotic stricture[12,19,29]. Balloon dilation of all strictures is not feasible because of the multiple diffuse locations of strictures[74]. The small caliber of the hilar and intrahepatic bile duct may limit the caliber and number of stents placed[74]. Furthermore, repeated accumulation of biliary sludge or casts gives rise to rapid stent occlusion, recurrent cholangitis, liver abscess, and biliary cirrhosis[19,32,74]. Patients with non-anastomotic stricture need more frequent and numerous ERC sessions and have a more prolonged time of response[3,38]. Although non-anastomotic stricture is more resistant and temporarily responsive to endoscopic treatment[5,36], this endoscopic strategy is able to delay retransplantation and to relieve the symptoms of cholangitis while waiting[19,74].

Bile leakage

ERC is the gold standard for diagnosis of any kind of bile leakage[31,36]. When ERC detects the exact site of biliary leakage, early prompt intervention should be performed, because bile leakage is an independent risk factor for the development of stricture[31]. Bile leakage is successfully treated with transpapillary ERBD stent placement, which bridges and seals the leakage[14,16,31,32,36]. Although sphincterotomy alone can be effective as a result of reducing pressure in the bile duct, to achieve a satisfactory result, ERBD stent placement typically should be used for diverting bile away from the leakage site[33]. Whether a bile leak occurs in an anastomotic or non-anastomotic site, the same approach can be used. Although clinical symptoms improve within a few days, complete resolution of the leakage occurs within 5 wk[5,13,63]. Most centers advocate that the stent should be left in place for about 2 mo, because of delayed healing

owing to the use of immunosuppressive agents[14,19]. In most cases, a total of 2 ERC sessions is sufficient for treatment of bile leakage[33]. If there is an associated biliary stricture, the strategy is careful balloon dilatation accompanied by ERBD stent placement beyond both the stricture and the leakage[14,31]. Bile leakage in a T-tube tract is often self-limiting and may be managed conservatively by leaving the tube open, without further intervention[31,34,36]. However, if persistent, endoscopic treatment should proceed such that ERBD stent placement occurs parallel to the T-tube, which is removed immediately after ERC[19].

Biloma
Any kind of bile leakage will result in biloma formation. ERC plays a therapeutic role in defining and eventually treating the underlying bile leakage[34]. If the associated biloma is symptomatically deteriorative, abundant, or infected, whether intrahepatic or perihepatic, the combination of endoscopic sphincterotomy with or without ERBD stent placement and simultaneous percutaneous catheter drainage is adequate and beneficial[14,32,36].

Bile duct stones, sludge, casts, debris and other filling defects
Biliary obstruction can also be caused by stones, sludge, debris, or casts after LDLT. The endoscopic management for these is similar to that for non-transplant patients; the obstructions are treated with various combinations of sphincterotomy and balloon retrieval or trapezoid basket extraction[18,31,35,36]. When biliary stricture is found, it should be treated simultaneously[19,33]. In the majority of filling defects, especially with stones, management is successfully accomplished in a single ERC session[14]. However, the endoscopic approach for cast extraction is less favorable for permanent clearance of the biliary tree[19,34]. In some cases, only a reduction of intraductal pressure by endoscopic sphincterotomy can be sufficient to achieve a favorable outcome. Large balloon dilation of the biliary sphincter orifice (EPBD, endoscopic papillary balloon dilation), with or without sphincterotomy, is reported to be a possible method for the removal of large stones and casts after LDLT, with improved efficacy and minimized complications[11,12,14].

Sphincter of Oddi dysfunction
Sphincter of Oddi dysfunction is defined as dilatation of the bile duct without stenosis or filling defects, along with biochemical cholestasis[14,36]. It is assumed that operative denervation of the distal common bile duct causes impaired ampullary relaxation and hypertonic sphincter, which may trigger biliary leakages by increasing the intraductal pressure[34]. However, it can be also expected to arise from a combination of posttransplant edema and inflammatory stricture due to long-term ERBD stent placement[19]. Patients are further evaluated with ERC, ideally with manometry[14,36,65].

Although manometry is essential to confirm the diagnosis, it is rarely performed because of the high risk of post-ERC pancreatitis[19], Instead, as long as patients present with symptoms and signs highly suspicious for the condition, endoscopic treatment is initially attempted by endoscopic sphincterotomy, transpapillary stenting, or both[14,19,33,34,65,75].

SPECIAL TECHNIQUES OF ENDOSCOPIC MANAGEMENT

Endoscopic naso-biliary drainage insertion
Occasionally, instead of an ERBD stent, an endoscopic naso-biliary drainage (ENBD) tube can be used to treat biliary complications, particularly with respect to bile leakage. When bile leakage is confirmed by ERC, ENBD is inserted proximal to the leakage site[9,11,12,22,27,35]. The ENBD removed after fluoroscopic testing has confirmed resolution of the leakage. Some centers have used ENBD to manage biliary stricture, as a bridge therapy for further inside-stent placement. In case of difficulty in adequate balloon dilatation or biliary stent insertion on the first attempt, ENBD is tentatively placed, followed by replacement with an inside-stent within 1 wk[11,66,67]. The advantage of ENBD is that it permits frequent ERC follow-up and easy retrieval without the need for additional endoscopic intervention[19,31]. However, the disadvantages of ENBD stenting are patient discomfort caused by the indwelling tube, prolonged hospital stay, and body fluid loss caused by non-physiologic bile drainage[19].

Inside-stent placement without endoscopic sphincterotomy
In conventional endoscopic procedures, especially multiple biliary stenting, sphincterotomy is generally performed, because the distal ends of the stents exposed to the duodenum compress the pancreatic orifice, which can lead to acute pancreatitis[12,41]. However, sphincterotomy induces regurgitation of the duodenal fluid into the graft bile duct and causes reflux cholangitis and frequent stent occlusion[76]. For these reasons, some groups have employed inside-stent placement without performing sphincterotomy in the treatment of biliary stricture after LDLT[12,41,67]. The inside-stent is a modified plastic stent placed above the intact sphincter of Oddi[67]. A distal flap of the stent is removed to facilitate transport into the bile duct, and a nylon thread is attached to the distal side, dropping into the duodenum to permit easy removal[67]. This procedure provides several benefits, including a lower risk of cholangitis and less frequent stent occlusion with long-term patency, by preserving the function of the sphincter of Oddi[41,67]. Additionally, as many as three 10 F inside-stents can be placed, because the distal ends of the stents do not compress the pancreatic orifice[41].

Deep enteroscopy technique: Patient undergoing Roux-en-Y choledocojejunostomy

When posttransplant biliary complications develop in patients who have previously undergone Roux-en-Y choledochojejunostomy or gastric bypass, conventional ERC with a duodenoscope is essentially impossible, because passage of an endoscope through the afferent loop of a Roux-en-Y reconstruction is problematic[77]. In these cases, a percutaneous transhepatic approach is recommended as the initial treatment modality. However, new developments in deep enteroscopy techniques allow successful endoscopic access to the biliary orifice and anastomosis site[14,38,77-81]. Initially, the deep enteroscopy technique employed a variable stiffness colonoscope, such as a pediatric colonoscope[14]. Recently, single-balloon enteroscopy, double-balloon enteroscopy, and spiral overtube-assisted enteroscopy have been used[14,38]. In double-balloon enteroscopy, a balloon-attached enteroscope is passed through a balloon-attached overtube, and is advanced retrograde through the duodenum, jejunum, and up a Roux limb by alternate inflation of the two balloons[80]. If applying a spiral overtube, it is installed over the enteroscope. As the spiral overtube is rotated, the small bowel is pulled onto the overtube, eventually allowing the enteroscope to advance through[14]. Once the biliary anastomosis site is observed, ERC is performed under direct vision through the enteroscope, and adequate therapeutic intervention is subsequently achieved. Several studies have reported the successful balloon dilatation of biliary strictures with the use of a deep enteroscopy technique in patients undergoing Roux-en-Y choledochojejunostomy[80,82,83]. A few studies support a more invasive approach on endoscopic management for posttransplant biliary complications in patients with an extremely long Roux limb, including performing a percutaneous gastrostomy or jejunostomy tube insertion, followed by enteroscopic access through it[77,84].

Rendezvous technique

Occasionally there are cases where conventional endoscopic access is unsuccessful. In these failed situations, alternative treatments should be considered to facilitate cannulation of the bile duct. Cannulation of a biliary stricture can be achieved by means of the rendezvous technique, which is a hybrid technique combining percutaneous transhepatic and endoscopic transpapillary approaches[20,38,81,85-94]. When a guide-wire cannot pass over the stricture by ERC, after performing percutaneous transhepatic cholangiography (PTC) and percutaneous transhepatic biliary drainage (PTBD) catheter placement, a guide-wire is inserted through PTBD tube and is advanced into the duodenum. Once the guide-wire exits the papilla, the wire is captured by the endoscopic Dormia basket, forceps, or snare introduced through ERC, and then is pulled through the biopsy channel of the endoscope[90]. Through

the guide-wire, the subsequent ERC procedures are followed. This technique is recommended in patients with a sharp or twisted angle at the stricture site[86,91]. Depending on hospital policy, both parts of the technique can be performed simultaneously in the fluoroscopy unit by both an interventional radiologist and endoscopist[93], or they can be performed sequentially[85].

In addition to this classical method, various modified Rendezvous techniques have been attempted. Many have performed a pushing insertion of the guide-wire from the common bile duct into the lumen of a bottle-top metal-tip ERC cannula, instead of capturing the guide-wire with a basket or snare, and then the ERC cannula is advanced over the wire into the bile duct[20,24,86,90,94]. Another approach uses a Kumpe catheter instead of a guide-wire, because the Kumpe catheter's short length allows for easier manipulation and its slightly angulated end permits easy approximation to the ERC cannula[20]. Another approach is to use a microcatheter with a smaller wire[94]. Furthermore, in patients with complete stricture, a modified technique where the capture of guide-wire occurs in the subhepatic space, not in the duodenum, has been performed successfully[91]. In this approach a guide-wire is inserted *via* ERC, puncturing into the paracholedochal space. The snare is inserted through PTC into the duodenal bulb to catch the guide-wire and pull it through to the outside of the body, establishing bilio-duodenal continuity[91]. Many studies have demonstrated that the rendezvous technique is useful and safe for the management of biliary stricture after LDLT with duct-to-duct anastomosis[20,38,86-88,91,94]. Owing to these advances, the Rendezvous technique combined with double-balloon enteroscopy has been introduced for the treatment of biliary anastomotic obstruction after LDLT with Roux-en-Y anastomosis[81,92]. Some reports support the application of the rendezvous technique for the treatment of bile leakage and biliary anastomotic disruption[85,89,93]. When a previous ERC or PTC approach to place a stent across the leak site has failed, bile duct continuity can be restored using the modified rendezvous technique, where the grasping of a guide-wire occurs at the biloma[85,93].

Magnetic compression anastomosis technique

Magnetic compression anastomosis is another hybrid technique, which is used for recanalization of severe biliary strictures after LDLT that cannot be treated with conventional methods[95-100]. This technique can be applied to completely obstructed or disconnected biliary strictures[96]. For this procedure, two magnets are introduced on each side of the obstructed bile tract: the first magnet (parent magnet, without wire) is delivered in a transpapillary approach at the inferior site of obstruction through ERC, and the second (daughter magnet, attached with a 30 cm nylon wire) is positioned at the superior site of obstruction through

the PTBD[99]. The two magnets are approximated to within 2.5 to 4 cm distance under fluoroscopic guidance, if necessary, using a balloon catheter for better advancement[97]. The two magnets are immediately attracted toward each other, sandwiching the stricture[100]. The transmural compression of the two magnets causes gradual ischemic necrosis, and thus creates a new anastomosis between the magnets[6,99]. If a re-anastomosis is successfully formed, the approximated magnets will naturally pass along the bile tract[97], or else each magnet is respectively pulled out *via* the ERC and PTBD routes[101]. Finally, after confirming the recanalization, a temporary ERBD stent is positioned across the stricture. Graphic illustration describing the process of magnetic compression anastomosis technique for severe biliary stricture is presented in supplementary material (Supplementary Figure 1). The magnets used for this technique are cylindrical samarium-cobalt rare-earth magnets because of their stronger retention force[102]. Routinely, the parent magnet (5 mm, 3700 gauss) has a larger diameter and greater strength than the daughter magnet (4 mm, 3200 gauss). In this way the daughter magnet is continuously pulled, and the pair of magnets can easily move into the distal bile duct and intestine, not into the proximal bile duct, once re-anastomosis is established[99].

The clinical feasibility, safety, and usefulness of the magnet compression duct-to-duct anastomosis technique have been established and demonstrated in various recent reports of severe biliary stricture or obstruction after LDLT[95-98,100]. Recently, owing to these advances, a number of reports applied the magnetic compression duct-to-enteric anastomosis method for biliary stricture in patients undergoing Roux-en-Y choledochojejunostomy[99]. They created an anastomosis between the bile duct and the small intestine, using a forward-viewing endoscope or constructing a temporary skin-intestinal fistula to carry the parent magnet near the stricture[99,101]. Additionally, several technical modifications have been made in the magnetic compression anastomosis technique in recent innovative studies. Some reported the usefulness of prior insertion with a covered, retrievable, self-expanding metallic stent through ERC, where the parent magnet is delivered safely through the stent to the stricture site[24,95,97,103]. Another pioneer used an overtube with an ERC endoscope to keep the magnet in the initial position while delivering the magnet through the stomach to the bile duct[97]. They also produce a newly designed magnet with 50% greater magnetic power and a smaller diameter than the previous magnet, to enable to access into narrow bile ducts[97]. One study reported a case in which a bile duct branch was left without anastomosis and was later successfully anastomosed to the cystic duct stump in a second-look fashion using a magnetic compression anastomosis technique[103].

Although re-anastomosis depends on the distance between the two magnets and the strengths of the magnets[97,101], complete recanalization of posttransplant biliary obstruction requires nearly 1 mo[104]. Nonetheless, this technique can prevent the need for a lifelong external drainage bag and reduce the chance of requiring reoperation for severe biliary stricture after LDLT[97].

Direct cholangioscopy technique: Single-operator peroral cholangioscopy

When a biliary stricture is severe and too tight to access by a conventional ERC procedure, a direct cholangioscopy technique is valuable for successful guide-wire placement. In particular, the most recent and desirable approach is single-operator peroral cholangioscopy using the SpyGlass® Direct Visualization System (Boston Scientific Corp.)[14,38,46,75,105,106], in which a single endoscopist operates both scopes with 4-way tip deflection, in contrast to traditional dual-operator cholangioscopy. Recent studies have indicated that single-operator peroral cholangioscopy is feasible and can be successfully performed in LT recipients with biliary complications[14,75,105-107].

Direct cholangioscopy allows direct visualization of the inner wall of the bile ducts, and a pinhole orifice can be visualized at the stricture site[38,105]. Under direct cholangioscopic vision, a guide-wire can be passed through the orifice and placed across the tight stricture[38,105,106]. Direct visualization may also facilitate evaluation of indeterminate biliary strictures or other biliary complications in LDLT recipients requiring ERC[14,75]. Additionally, direct cholangioscopy enables one to employ advanced intraductal therapeutic maneuvers, such as tissue acquisition for sampling purposes and complete clearance of large or difficult stones, all of which are limitations of conventional ERC techniques using only contrast-mediated fluoroscopic imaging[14]. A limited number of studies indicate innovative management of biliary stricture guided by single-operator peroral cholangioscopy in LDLT[105,106]. A recent case report introduced methylene blue-aided peroral cholangioscopy to optically diagnose the ischemic-type of biliary lesions after transplant[107].

NEW TYPES OF ENDOSCOPIC DEVICES: BALLOONS AND BILIARY STENTS

The selection of an endoscopic treatment method depends on the characteristics of the lesion, including its etiology, location, severity, and findings from ERC imaging. The number, size, and form of the endoscopic devices are determined based on various treatment method options. The increasing development of endoscopic accessory devices, including cannulation catheters, balloons, guide-wires, and stents, will play a significant role in the management of biliary complications after LDLT.

Novel endoscopic balloons

A few preliminary investigations showed that a peripheral cutting balloon is more effective in the treatment of resistant biliary strictures not responsive to standard high-pressure balloon dilatation, with a proven two-year primary patency rate of 55% and secondary patency rate of 78%[108,109]. Furthermore, the use of paclitaxel-eluting balloons has been introduced as a new treatment option of biliary anastomotic stricture after liver transplant, which achieved a sustained clinical success of 92%[110]. Paclitaxel, as a mitotic inhibitor, has an antifibrotic effect, and the combination of dilation and antiproliferative therapy is reasonable to resolve biliary strictures characterized by fibroproliferation[111]. These balloons are known for their safety and efficacy in the treatment of arterial stenosis. Albeit from a preliminary investigation, these innovate results may offer several advantages in the field of LDLT.

Selection of biliary stents

The most commonly used ERBD stent is a plastic (polyethylene) stent. Plastic stents are easy to insert and more cost effective, but have a small diameter and can become clogged over time. Because of the prolonged dilatation and high risk for occlusion, the strategy of multiple side-by-side plastic stents placement has been generally accepted as the standard endoscopic treatment of biliary stricture after LDLT. Despite the excellent outcomes described above, there is often a need for frequent ERC to replace clogged ERBD stents, and repeated ERC interventions can be associated with ERC-related risks, such as pancreatitis, cost, and patient burden[73].

To reduce the recurrence of biliary stricture and to maintain a longer duration of patency, a metal stent with a larger diameter has been developed[15]. Traditional metallic open-mesh and uncovered metal stents normally cannot be removed, and are considered a permanently implantable device[112]. Over time, stent metal penetrates the submucosa of the bile duct, with consequent mucosal hyperplasia and ingrowth that promotes frequent stent occlusion and stone formation[14,112]. Removal of an embedded stent leads to infection, bleeding, and perforation. Therefore, these stents are typically contraindicated in benign biliary diseases, including posttransplant biliary stricture after LDLT[25,113-115].

In this setting, the covered, self-expanding metal stent, either partially covered or fully covered, has been introduced[70]. Because the outer coating of the stents prevents tissue ingrowth into the stent mesh[14], covered metal stents have less epithelial hyperplasia, less occlusion, and extended patency. Furthermore, it is retrievable. In contrast of uncovered metallic stents, which are difficult to remove and typically require a combination of techniques, removal of a covered metallic stent with a snare is relatively simple and safe,

and can be followed immediately by further endoscopic therapy[112].

There is an experience in temporary placement of partially covered, self-expanding metal stents to maintain stent patency, with success rate of 94%[112]. However, the placement of partially covered metal stents, while effective in the initial treatment of biliary stricture, have limited long-term efficacy[16]. Stent extraction is sometimes difficult or impossible due to the inflammatory reaction in the upper and lower non-covered ends[70]. As a result, although it is applicable theoretically, the use of partially covered self-expanding metal stents cannot be recommended for therapy of posttransplant biliary stricture.

Instead, a recently developed, fully covered, self-expanding metal stent has emerged as a good alternative in the management of posttransplant biliary complications, especially in patients not responding to standard endoscopic treatment[14,16,53,70,116-119]. The lack of embedding of the metal into the bile duct wall allows for easier removability overall[116]. The diameter of this stent is 10 mm, about three times as large as the diameter of the average plastic stent[70]. The stent is attached to a long retrieval string, and can be removed a couple of months later by grasping the string with a standard forceps[117]. Several studies have reported that temporary placement of a fully covered, self-expanding, metal stent is feasible and effective in the treatment of refractory biliary stricture after LDLT, showing a success rate of 60% to 87.5%[14,16,53,70,117,119]. The use of a fully covered, self-expanding metal stent provides a larger stricture dilatation, longer stent patency, fewer ERC sessions and its attendant benefits, such as fewer adverse events, shorter hospital stays, and reduced costs[16,53,70]. Similar to biliary strictures, other studies have found this stent to be effective in the treatment of persistent bile leakage considered difficult to treat[14,16]. Although acceptable benefits have been proven, one of the limitations of this stent is the tendency to migrate out of or inside the bile duct, occurring in up to 37.5% of cases[14,70]. Downstream migration inside the bile duct is a more serious complication. To overcome this disadvantage, a few techniques are suggested, including placement of the stent entirely above the papilla[14] and use of a modified stent with convex margins and an anti-migrating waist on the central portion[120]. Currently, the temporary placement of a fully covered, self-expanding, metal stent can serve as a rescue treatment, rather than as a first-line therapy, in patients with biliary complications after LDLT that have failed other management techniques[119]. In the near future, the use of self-expanding stents made of biodegradable material may further contribute to improved endoscopic therapy for posttransplant biliary complications, through the influence of longer patency, lower biofilm buildup, and an enhanced antiproliferative effect with a single intervention[104,121].

ENDOSCOPIC MANAGEMENT OF BILIARY COMPLICATION IN DONORS

Biliary complication after LDLT may occur in the donor as well as the recipient. With the increasing number of LDLT, living liver donors are also at increased risk for biliary complications. The most common postoperative complication among donors for LDLT is a biliary complication[122]. The overall incidence of biliary complications in living liver donors ranges from 2.5% to 15%, with bile leakage being the most common[6,7,122-128]. In a multicenter study of 393 donors in the United States, 9.2% of donors had bile leakage and 0.5% had biliary stricture[126]. Biliary complications are seen more commonly with right lobe donation[122,127,128]. According to a survey in five Asian centers, among 561 right lobe donors, 6.1% had bile leakage and 1.1% had biliary stricture[128]. In another series of 207 right lobe grafts, 13.0% of donors experienced biliary complications, including a single death after uncontrolled bile leakage[7]. A national survey in the United States found that 6% of right lobe donors had biliary complications requiring intervention[129].

ERC is a good modality for diagnosis and treatment of postoperative biliary complications in living liver donors[127]. The general principles of endoscopic management in donors are similar to those of the recipients, and outcomes are also quite similar. A study of 731 consecutive patients who donated liver grafts for LDLT demonstrated that most donors (80%) with biliary complications were successfully treated by endoscopic treatment[122].

Bile leakage in donors usually presents within 2 wk of surgery[32]. Minor bile leakage can be successfully managed with conservative therapy, as leaks resolve spontaneously as long as an adequate surgical drain is placed[127]. When bile leakage is not cured conservatively, endoscopic management is effective, and should be attempted as the first-line therapy[122,127]. In one study, 9 of 74 donors (11.2%) had bile leakage, 6 of whom were managed endoscopically with temporary ERBD stent placement, recovering uneventfully[130]. Another study observed that 7 of 276 donors (2.5%) developed bile leakage, and in 6 of these donors, bile leakage resolved within an average of 15 d after placing an ENBD tube across the site of the leak[127].

Biliary stricture in donors occurs less frequently compared with recipients[38], and develops often in donors who had bile leakage immediately after LDLT[127]. ERC followed by endoscopic balloon dilatation and biliary stent placement is the mainstay of treatment. In one study, all donors with biliary stricture demonstrated a satisfactory improvement by ERBD for an average of 113 d[127]. Interestingly, biliary stricture can be more difficult to manage after right lobe donation[32], because the compensatory hypertrophy and right rotation of the remnant left lobe may play a role in the development of bile duct distortion and deformity[127]. Some studies found that the angle between the common hepatic duct and the left hepatic duct is more acute in donors with biliary stricture than in those without stricture[122,127]. A recent report described the use of the magnetic compression anastomosis technique in a donor with biliary stricture after left hepatectomy for LDLT[131]. In addition, when endoscopic attempts have failed due to inaccessibility to guide-wires, the rendezvous technique may be helpful in the placement of a biliary stent, even in living right liver donors[89].

ENDOSCOPIC MANAGEMENT OF BILIARY COMPLICATIONS AFTER PEDIATRIC LIVER TRANSPLANTATION

Biliary complications occur among pediatric LDLT, and they are certainly associated with increased morbidity and mortality. Rather, biliary complications are more prevalent in the pediatric transplant population due to the small caliber of the bile duct and vascular structures[132,133]. Like adult transplant patients, partial liver graft has a higher risk of biliary complication than whole graft in pediatric liver transplantation[134]. According to a multicenter database from the Studies of Pediatric Liver Transplantation (SPLIT) registry, the incidence of biliary complications within 30 d after pediatric LDLT is 17.5%[135]. The most common complications are bile leakage and biliary stricture[132,135,136]. In one series, 33% of pediatric LDLT recipients had biliary complications, and the incidence of biliary stricture and bile leakage is estimated to be 17% and 20%, respectively[137]. In another recent series, 6.3% of biliary complications overall are observed in pediatric LDLT, with bile leakage and anastomotic stricture occurring in 1.9% and 4.5%, respectively[138].

In pediatric LDLT, Roux-en-Y choledocojejunostomy is mainly performed for biliary reconstruction because the recipient bile duct is relatively small or because of the presence of underlying liver disease[24,80,132]. In patients who have biliary atresia and who have had a prior Kasai hepatoportoenterostomy operation, the Roux-en-Y choledocojejunostomy is mandatory[132]. As a result of this anatomical cause, the biliary tree is inaccessible to endoscopy in most cases[136] and the success rate of ERC is low[80]. Although the role of ERC treatment for biliary complications has been demonstrated in adult LDLT cases and is considered first-line therapy[11,63], therapeutic ERC has not been widely accepted in pediatric LDLT cases[136]. Recently, however, endoscopic techniques that go beyond previous conventional ERC have been developed, allowing successful endoscopic access. Evolved ERC and endoscopy-based methods can be applied to pediatric patients, thus enabling endoscopic treatment

of posttransplant biliary complications with satisfactory outcomes[80,81,83,136,139,140].

Some studies described successful enteroscopic balloon dilation of biliary anastomotic strictures after pediatric LDLT with Roux-en-Y choledocojejunostomy by using double-balloon enteroscopy[80,83,140]. In one of those studies, the rate of the enteroscope reaching the biliary anastomotic sites was 68.0%, and the success rate of enteroscopic balloon dilation was 88.2%[83]. In these, if anastomotic stricture recurred, enteroscopic intervention was repeated and a biliary stent was placed in all of these patients. Double-balloon enteroscopy has become a less invasive, safe, and effective therapeutic option that permits periodic endoscopic intervention. A novel case reported the rendezvous technique using double-balloon enteroscopy for complete anastomosis obstruction of hepaticojejunostomy after pediatric LDLT: One approach from the bile duct was performed by 2.8-mm-diameter cholangioscopy through a PTBD tube, and the other approach from the jejunum was performed by double-balloon enteroscopy[81]. Another case highlighted endoscopic treatment with the use of an interventional cardiovascular-based smaller caliber guide-wire and angioplasty balloon in a pediatric LDLT recipient with a biliary anastomotic stricture[139]. A recent retrospective study demonstrated that ERC was feasible and successful in the diagnosis and treatment of posttransplant biliary complications among pediatric LDLT recipients[136]. In their ERC procedure, a video duodenoscope was used in pediatric patients with duct-to-duct biliary anastomosis, and a pediatric colonoscope was used for push-enteroscopy in patients undergoing a Roux-en-Y choledocojejunostomy. Following the principles for adult LDLT recipients with biliary complications, minimally invasive and effective ERC treatment can be used in pediatric LDLT recipients whenever endoscopic access to the biliary tree can be obtained[136].

SUCCESS RATES AND OUTCOME PREDICTORS OF ENDOSCOPIC MANAGEMENT

The treatment of posttransplant biliary complications can be achieved most optimally through diverse endoscopic strategies. The role of endoscopy in this field is unequaled. Currently, the preferred endoscopy method is ERC, followed by therapeutic interventions such as endoscopic sphincterotomy, balloon dilation, stent placement, or stone extraction as indicated. Several studies have recently reported high success rates and factors associated with outcomes in endoscopic management of biliary complications. Table 1 summarizes the results of endoscopic therapeutic options for these biliary complications following adult LDLT. Despite the heterogeneity of the study designs, the evidence shows that endoscopic management is efficient, guarantees an acceptable clinical outcome, and avoids the need for surgical or percutaneous transhepatic approaches in the majority of patients with biliary complications related to LDLT.

The reported success rate of endoscopic management for biliary anastomotic stricture after LDLT is highly variable, depending on the complicating etiology and technique, and ranges from 64% to 76%[11,12,16,40,41,43,59]. To be more exact, this rate is the initial technical success rate of the first endoscopic intervention. The final therapeutic success rate of endoscopic treatment ranges from 45% to 93%, with recurrence rates from 13% to 44%, varying according to the follow-up period. Therapeutic success means complete resolution without need for further endoscopic, surgical, or percutaneous procedures for the management of biliary problems. Generally, to achieve resolution of the anastomotic stricture, most patients require multiple ERC sessions, averaging 2.7 to 5.4 per patient, multiple stents of 1.9 to 2.5 per ERC, and stent exchange every 2 to 3 mo[47,73]. Recurrent strictures are also successfully retreated with the same endoscopic methods. Meanwhile, although non-anastomotic stricture is much less frequently observed after LDLT, the endoscopic management of non-anastomotic strictures achieves a much worse success rate of 25% to 30%, with a higher recurrence rate[12,29,59,141]. Non-anastomotic stricture is more resistant to endoscopic treatment because of repeated sludge accumulation, frequent and rapid stent clogging, and a resultant demand for multiple procedures. Furthermore, endoscopic dilation and stent placement of multiple hilar and intrahepatic stenosis is technically more difficult[14]. In contrast, endoscopic methods have better success in the management of bile leakage, with a reported resolution rate of 69% to 100%[11,18,22,35,58]. This result varied widely depending on whether the bile leaks from a cut surface or from the anastomotic site. According to a recent report from the A2ALL consortium[13], 92% of LDLT recipients with bile leakage resolved their leaks within 6 mo of diagnosis. The median time to tube, stent, and drain-free status after a bile leakage was 1.3 mo. Compared with bile leakage, the probability of resolution of biliary stricture was lower among LDLT recipients. Nevertheless, at 24 mo after diagnosis, 94% of LDLT recipients with biliary stricture were tube, stent, and drain-free.

Despite the high success rates presented, endoscopic intervention in LDLT patients is a technical challenge, mainly because of the complexity of biliary reconstruction[11,14,31,36]. The bile duct anastomosis in LDLT is small in diameter, more tortuous, sharply angulated, twisted, located proximal to the hilum, and sometimes kinked at the hilar portion, which probably results from fibrosis around the anastomosis and from compensatory hypertrophy of the transplanted liver[6,43,59]. The small caliber of the donor duct limits the size and number of biliary stents used[14,59]. The distorted bile duct makes an endoscopic approach

Table 1 Results of endoscopic management of biliary complications after adult living donor liver transplantation: A review of the literature

Ref.[1]	Type of biliary complication	Initial technical success, n (%)[2]		Final therapeutic success, n (%)[3]		Recurrence at a mean follow-up months, n (%)[4]	Endoscopic treatment modality	Number of ERC session per patient[5]	Duration for final success (mo)[5]	Factors affecting endoscopic treatment outcomes
Hisatsune *et al*[41] D-D	Stricture	14/22	(63.6)	2/14	(14.3)	-	IS	1	12	Number of the proximal duct at D-D
Shah *et al*[35] D-D	Stricture	3/4	(75.0)	3/3	(100)	-	BD and/or PS	1.5	2.3	
	Leakage	8/8	(100)	8/8	(100)	-	PS with/without ES	2	1.4	
Zoepf *et al*[26] D-D	Stricture	7/12	(58.3)	7/7	(100)	1/7 (14.3) at 10.0	BD and/or PS	3.5	8	
Yazumi *et al*[12] D-D	Stricture	48/75	(64.0)	28/55	(50.9)	3/28 (10.7) at 1.8	IS with/without BD	-	9	Crane-neck deformity
	Leakage	13/16	(50.0)	8/13	(61.5)	-	ENBD	-	0.6	Non-anastomotic stricture
Tsujino *et al*[11] D-D	Stricture	12/17	(70.6)	9/12	(75.0)	4/9 (44.4) at 10.1	BD with ENBD/IS	4.1	-	
Lee *et al*[22] D-D	Stricture	12/17	(70.6)	7/14	(50.0)	0/7 (0.0) at 13.1	BD with ENBD/PS	3.9	7.2	Stricture Sharp angulation of D-D
	Leakage	11/13	(84.6)	9/11	(81.8)	0/9 (0.0) at 13.1	PS or ENBD	2.2	3	Concomitant bile leakage
Tarantino *et al*[16] D-D	Stricture	14/20	(70.0)	7/14	(64.3)	-	BD with double PS	3.4	-	Continuous bile leakage despite PS
	Leakage	11/13	(33.3)	3/4	(75.0)	-	ES with PS	2.3	-	Persistence of stricture after 1 yr
	Both	4/6	(66.7)	0/4	(0.0)	-	-	-	-	
Kato *et al*[59] D-D	Stricture	31/41	(75.6)	28/35	(80.0)	7/28 (25.0) at 9.3	BD with PS	4	14.5	Concomitant bile leakage
Kim *et al*[40] D-D	Stricture		-	38/60	(63.3)	5/38 (13.2) at 7.9	BD with PS	3	-	Shape of distal duct at D-D: pouched
Kobayashi *et al*[66] D-D	Stricture		-	7/16	(43.8)	-	-	-	-	Delayed diagnosis of stricture
Seo *et al*[43] D-D	Stricture	15/26	(57.6)	20/29	(68.9)	6/20 (30.0) at 28.0	BD with PS	2.3	6.8	Late onset over 24 wk Delayed diagnosis of stricture Short duration of biliary stenting
Gómez *et al*[18] D-D	Stricture	4/10	(40.0)	2/4	(50.0)	-	BD with/without PS	2	-	
	Leakage	3/4	(75.0)	3/3	(100)	-	ES with/without PS	3	-	
Chang *et al*[28] D-D	Stricture	63/101	(62.4)	48/90	(53.3)	-	BD with PS	3.2	11	Non-anastomotic stricture Hepatic artery stenosis
Lee *et al*[23] D-D	Stricture	64/137	(46.7)	38/68	(55.9)	-	PS or ENBD	4.8	-	Stricture-to-ERC interval Morphology of stricture : narrow, separate duct, nonvisualized Shape of distal duct at D-D: round tip
Kim *et al*[61] D-D	Stricture	82/147	(55.8)	52/141	(36.9)	6/52 (11.5) at 21.1	BD with PS	6.3	12.7	Early onset within 1 yr after LDLT
Yaprak *et al*[58] D-D	Stricture		-	7/13	(53.8)	-	-	-	-	Long length of stricture
	Leakage		-	5/7	(71.4)	-	-	-	-	More than 1 bile duct anastomosis
Chan *et al*[142] D-D	Stricture	8/8	(100)	6/8	(75.0)	0/6 (0.0) at 3.0	BD with PS	4.7	4.2	Disuse of intraoperative biliary stent
Kurita *et al*[67] D-D	Stricture	94/118	(79.7)	81/92	(88.0)	8/81 (9.9) at 53.0	BD with IS	1.4	6.3	Use of ES
Hsieh *et al*[71] D-D	Stricture	32/38	(84.2)	38/38	(100)	8/38 (21.1) at 9.45	BD and maximal PS	4	5.3	Right lobe liver graft High-grade stricture Sharp angulation of D-D Conventional PS *vs* maximal PS
Chok *et al*[37] D-D	Stricture		-	41/56	(73.2)	-	BD with/without PS	3	-	Younger recipient age Longer operation time Shape of distal duct at D-D: pouched Initial bile leakage

Na et al[24] D-D	Stricture	53/65 (81.5)	112/129 (86.8)	-	BD and maximal PS	3.2	-	Early period of transplant experience
		-	59/64 (92.2)	-	Rendezvous	-	-	
Chang et al[86] D-D	Stricture	20/20 (100)	13/20 (65.0)	-	Rendezvous	2	7.2	Sharp or twisted angle at stricture
Mita et al[77] C-J	Stricture	7/22 (31.8)	-	0/7 (0.0) at 13.3	BD (deep enteroscopy)	2	2.5	Tube jejunostomy in long Roux limb
Kamei et al[82] C-J	Stricture	5/9 (55.6)	7/9 (77.8)	4/7 (57.1) at 27.6	BD (deep enteroscopy)	2.1	-	Use of a single ERC intervention
Jang et al[97] D-D	Stricture	10/12 (83.3) : magnet approximation	10/10 (100) : recanalization 9/10 (90.0) : stent-free	1/9 (11.1) at 3.3	Magnetic compression anastomosis	-	2.5 6.1	Length of stricture LDLT-to-ERC interval Architecture of the bile duct Strength of the magnet

[1]References: Author, Type of biliary reconstruction in study population; [2]Initial technical success, n (%): patients who underwent successful ERC intervention/patients receiving a first session of ERC (excluding prior transhepatic rendezvous); [3]Final therapeutic success, n (%): patients who achieved cholangiographic resolution without need for further endoscopic, surgical, percutaneous procedures (*e.g.*, stent-free) / patients treated by ERC interventions; [4]Recurrence, n (%): patients with recurrent biliary problems with cholangiographic evidence and the need for subsequent intervention/ patients who resolved; [5]Values are expressed as mean. BD: Balloon dilatation; C-J: Biliary anastomosis with Roux-en-Y choledochojejunostomy; D-D: Duct-to-duct biliary anastomosis; ENBD: Endoscopic nasobiliary drainage; ERC: Endoscopic retrograde cholangiography; ES: Endoscopic sphincterotomy; IS: Inside-stent placement above the intact sphincter of Oddi; PS: Plastic stent placement.

difficult. Several studies have reported that the most common reason for failure of endoscopic treatment is the inability to pass the guide-wire through the anastomotic site[12,41,43,54,61,142]. Moreover, in cases with multiple duct anastomosis or ductoplasty, it may be very difficult to navigate each branch with a guide-wire[59]. In case of anastomosis constructed near the hilum with a short distance from the second branch, guide-wire passage is infeasible[43,59].

Recently, numerous studies have identified factors predicting failure of primary ERC interventions. It is a foregone conclusion that endoscopic intervention will be unsuccessful for non-anastomotic strictures or ischemic biliary lesions accompanying hepatic artery complications[12,28]. One study reported that repeat surgery for a non-biliary indication in the first posttransplant month is a predictor of endoscopic management outcome, since that is potentially related to ischemia[47]. Concomitant bile leakage also contributes to ERC failure[16,22,59]. When bile leakage is present, the anastomotic site may be obscured by the leaking of contrast material, precluding passage of a guide-wire[59]. The LDLT-to-ERC interval or stricture-to-ERC interval has an impact on ERC failure[23,43,61]. The rate of failure of primary ERC therapy is high in patients with late onset and delayed diagnosis of biliary stricture after LDLT. Many studies have demonstrated that failure of a primary ERC is associated with cholangiographic findings, such as the morphology of the stricture, shape of the distal duct tip, and the angle between the proximal and distal bile ducts[12,22,23,25,37,40]. Narrow strictures or separate duct type strictures have a higher failure rate than do wide strictures. In nonvisualized strictures, endoscopic intervention often fails[23]. Pouched (round tip) distal strictures are the most difficult type to manage with endoscopic intervention[23,37,40]. Sharp angulation of

the anastomotic bile ducts is also a reported cause of ERC failure[12,22]. The most representative example is the crane-neck deformity, in which cholangiography shows a sharp angulation of the anastomotic stricture, characterized by a severely bent common bile duct that looks like a crane's neck[12]. In patients with an anastomotic stricture with a crane-neck deformity, because the biliary anastomosis is located far below the highest portion of the duct, endoscopic intervention is unsuccessful. Additionally, a study reported that strictures recur more frequently in patients with a shorter duration of stenting[43]. A report from the A2ALL consortium revealed that increased experience, with more than 15 biliary complications at a center, is directly associated with a significantly shorter time to resolution, indicating a learning curve for endoscopic management[13].

CONCLUSION

Despite consistent improvements in the overall outcomes of LDLT donors and recipients, the bile duct is still the most common site for postoperative complication, the so-called the Achilles' heel of LDLT[143]. Biliary complications after adult as well as pediatric LDLT occur commonly in both donors and recipients, and can lead to significant morbidity and even mortality unless successfully treated. With the majority of patients requiring long-term and repeated therapies, these make the management of biliary complications a major distress during the postoperative follow-up of donors and recipients. At present, these complications can be definitively treated and optimally managed through various endoscopic procedures, including sphincterotomy, balloon dilatation, multiple stent placement, and filling defects extraction. Although the outcome of endoscopic management depends on both

the etiology and location of the biliary complication, several recently published reports clearly demonstrate the safety, long-term efficacy, and superior outcomes of endoscopic therapy for biliary complications after LDLT. Recent technological developments, such as deep enteroscopy, direct cholangioscopy, magnetic compression, or removable fully covered, self-expanding metal stents, now allow for more transpapillary access and a better stenting effect. These developments are progressively expanding the scope and role of therapeutic endoscopy in LDLT patients with biliary complications. Based on these results, therapeutic endoscopy is recommended as a standard first-line approach, and percutaneous transhepatic and surgical modalities may serve as subsequent rescue procedures in failed or resistant cases of endoscopic therapy. In the future, more effective new endoscopic techniques with refined accessory devices will become available and be established to increase optimal results.

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