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REVIEW

Bile duct complications after liver transplantation

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Summary

Complications involving the biliary tract after orthotopic liver transplantation (OLT) have been a common problem since the early beginning of this technique. Biliary complications have been reported to occur at a relatively constant rate of approximately 10–15% of all deceased donor full size OLTs. There is a wide range of potential biliary complications which can occur after OLT. Their incidence varies according to the type of graft, type of donor, and the type of biliary anastomosis performed. The spectrum of biliary complications has changed over the past decade because of the establishment of split liver, reduced-size, and living donor liver transplantation. Apart from technical developments, novel diagnostic methods have been introduced and evaluated in OLT, the most prominent being magnetic resonance imaging (MRI). Treatment modalities have also changed over the past years towards a primarily nonoperative, endoscopy-based strategy, leaving the surgical intervention for lesions which otherwise are not curable. The management of biliary complications after OLT requires a multidisciplinary approach. Conservative, interventional, and endoscopic treatment options have to be weighed up against surgical re-intervention. In the following the spectrum of specific bile duct complications after OLT and their treatment options will be reviewed.

Introduction

Complications involving the biliary tract after orthotopic liver transplantation (OLT) have been a common problem since early beginning of this technique. Biliary complications have been reported to occur at a relatively constant rate of approximately 10–15% of all deceased donor full size OLTs [1–3]. There is a wide range of potential biliary complications which can occur after liver transplantation (Table 1). Their incidence varies according to the type of graft, type of donor, and the type of biliary anastomosis performed. According to the time of onset after OLT, biliary complications may be divided into early and late complications. Approximately two thirds of all biliary complications occur as early complications within the first 3 months after OLT, and are a significant source of morbidity and mortality [4]. An estimated one third of biliary complications occur within 1 month of surgery, and 80% within 6 months [4]. A variety of post-transplant biliary complications exist, but the most common are leaks and strictures. Leaks occur preferentially in the early post-transplant period, stricture formation typically develops gradually over several months to years. The annual incidence of biliary complications was reported to be <4% after the first post-transplant year [5].

The spectrum of biliary complications has changed over the past decade because of the establishment of split liver, reduced-size, and living donor liver transplantation (LD-LTx) (Table 2). The incidence of biliary complications in reduced-size liver transplantation was reported to be as high as 24% [6], however, approximately 50% of complications related to cut surface leakages. The initial experience with *ex-situ* split liver transplantation for infants and children was accompanied by an average biliary complication rate of 24–27% [7–9]; however, has been reduced from that markedly [10,11]. *In-situ* split-OLT was reported to result in lower complication rates of the biliary system of about 0–15% [12–14]. In pediatric recipients, a biliary complication rate of 8.7–15% was

Table 1. Specific biliary complications.

Bile leakage
Anastomotic leakage
Bile duct anastomosis
Bilioenteric anstomosis
Nonanastomotic leakage
T-tube related
Bile duct necrosis
Cut surface of reduced grafts
Bile collection (biloma)/biliary abscess
Bile duct obstruction
Extrahepatic obstruction
Anastomotic stricture
Extraanstomotic stricture
Intrahepatic stricture
Localized
Multiple
Papillary dyskinesia/ampullary dysfunction
Bile stones, sludge, and casts
Bile duct complications related to bilioenteric anastomosis
Anastomotic leakage
Intestinal perforation
Gastrointestinal bleeding
Cholangitis
Blind loop syndrome
Calcineurin inhibitor malabsorption
Others
Hemobilia
Mucocele

reported [15]. The incidence of biliary leaks and strictures for adult-to-adult right lobe LD-LTx was reported to be as high as 30% in the initial phase of clinical establishment; however, with the learning curve being overcome, biliary complication rates decreased to approximately 22% [5,16–22]. Several centers have recently reported an 8–14% biliary complication rate after right lobe LD-LTx (Table 2) [23–25]. Different facts may have contributed to these latter differences. Complications in the most recent studies may have been underestimated by only reporting complications requiring intervention. Additionally, there is no standardization of reports regarding complexity of biliary reconstruction. A relevant number of LD-LTx requires reconstruction of two or more orifices, thereby increasing complexity of surgery and complication rate as well. Therefore, donor selection may also influence biliary complication rates in LD-LTx.

Apart from technical developments, novel diagnostic methods have been introduced and evaluated in OLT, the most prominent being magnetic resonance imaging (MRI) [26].

Treatment modalities have also changed over the past years toward a primarily nonoperative, endoscopy-based strategy, leaving the surgical intervention for lesions which otherwise are not curable. In the following, the spectrum of specific bile duct complications after OLT and their treatment options will be reviewed.

Etiology of bile duct complications after OLT

In early bile leaks and anastomotic strictures, surgical/technical reasons such as suture-related insufficiencies or stenoses, T-tube dislodgement, and acute hepatic artery

Table 2. Biliary complications after deceased donor full size and adult living donor liver transplantation.

Reference	Year	Center	No. of OLT	Biliary complications (%) Overall	Leakages	Strictures
Deceased donor full size OLT						
Lerut *et al*. [61]	1987	Pittsburgh	393	13	11	5
Colonna *et al*. [36]	1992	Los Angeles	738		8	3
Neuhaus *et al*. [66]	1994	Berlin	300	9	0.3	3
Grief *et al*. [4]	1994	Pittsburgh	1792	12		
Verran *et al*. [60]	1997	Ontario	502	13.5	1.6	6.6
Adult living donor liver transplantation (right lobe)						
Marcos *et al*. [17]	2000	USA	275	18	–	–
Broelsch *et al*. [16]	2000	Europe	123	14.6	–	–
Testa *et al*. [62]	2000	Essen	30	26.6	26.6	3.3
Fan *et al*. [21]	2002	Hong Kong	74	26	6.6	20
Sugawara *et al*. [24]	2002	Tokyo	25	8	0	8
Chen *et al*. [22]	2003	Asia	766	17.8	7.3	10.5
Brown *et al*. [5]	2003	USA	449	22	–	–
Settmacher *et al*. [25]	2003	Berlin	50	14	12	4
Various type of grafts (right lobe, left lobe)						
Todo *et al*. [18]	2000	Japan	308	32	8.1	5.2
Miller *et al*. [20]	2001	New York	59	–	23.7	6.8
Lee *et al*. [117]	2001	Seoul	157	–	5.1	5.7

OLT, orthotopic liver transplantation.

thrombosis (HAT), which potentially leads to ischemic strictures unless the vascular flow is immediately reconstituted or adequate collateral blood flow exists [27–30], should be ruled out. Additionally, low-flow phenomena in the hepatic artery unrelated to the anastomosis may occur in the case of a pre-existing splenic artery steal syndrome, congenital or arteriosclerotic stenosis of the celiac axis, or intermittent stenosis of the celiac axis during inspiration by the arcuate ligament [31]. Further technical reasons may be related to the delicate vascular supply of the bile duct. Particularly excess dissection of periductal tissue during organ procurement which impairs the vascular supply of the donor's bile duct and the use of electrocautery for biliary duct bleeding control in both, donor and recipient may contribute. Additionally, excess tension on the ductal anastomosis [32,33], and active bleeding from the cut ends of the bile duct prior to anastomosis were identified as risk factors for biliary complications.

Several other contributing factors including ischemic and immunologic injury, preservation injury because of prolonged ischemia [34,35], ABO incompatibility, cytomegalovirus (CMV) and other causes of infection [3], age crossmatch, chronic ductopenic rejection, and also patients with a pretransplantation diagnosis of primary sclerosing cholangitis (PSC) [36] were identified and discussed. Antiproliferative immunosuppressants, such as rapamycin and mycophenolate mofetil, may further increase the incidence of biliary complications. Both the bile duct and the vascular endothelium were shown to be vulnerable to the damaging effects of humoral and cellular immune mechanisms. They finally lead to bile duct cell death and stricturing, either directly or because of a compromised vascular supply, and ultimately result in ischemic cholangitis [37].

Special attention should be paid to additional contributing factors influencing the incidence of nonanastomotic strictures (NAS). Guichelaar *et al.* [38] studied a total of 749 consecutive patients prospectively. Seventy-two patients (9.6%) developed NAS at a mean of 23.6 ± 34.2 weeks post-transplantation. Nonanastomotic biliary stricture formation resolved in only 6% of affected patients. Although patient survival was not affected, retransplantation and graft loss rates were significantly greater in recipients who developed NAS. In contrast to previous reports, a pretransplant diagnosis of HCV was associated with a low frequency of NAS formation. The incidence of NAS was independently associated with pretransplant diagnoses of PSC and autoimmune hepatitis. HAT, and prolonged warm and cold ischemia times were also independent risk factors for NAS formation.

The PSC recurrence rate was reported to be as high as 37% at a median of 36 months [39]. Multivariate analysis showed that being male (relative risk 1.2, 95% CI, 0.73–2.15) and an intact colon before transplantation (relative risk 8.7, 95% CI, 1.19–64.48) were associated with recurrence.

Specific biliary complications

Bile leaks

Bile leaks are common after OLT, and may complicate 1–25% of OLT performed [1,3]. (Table 2) They can be divided into early and late bile leaks. The term 'early' is used differently in literature, defining a time period of 1–3 months after OLT. Thus, reported complication rates may vary considerably, too.

The incidence of early postoperative bile leaks is reportedly unrelated to the type of biliary reconstruction [33]. One recent prospective, randomized trial of end-to-end versus side-to-side choledocho-choledodiostomy (CC) revealed no significant difference with regard to biliary complications [40]. Anastomotic leaks are caused primarily by ischemic necrosis at the end of the bile duct (most commonly the donor duct) or a technically unsatisfactory anastomosis, i.e. suturing technique that produced insufficiency. Nonanastomotic, non-T-tube related leaks often result from vascular insufficiency because of HAT or other compromises to the arterial perfusion [32].

Leaks from other nonanastomotic sites, i.e. around T-tubes or from the cut surface, are less likely to endanger the graft or patient. The majority of early bile leaks after OLT are related to the elective or inadvertent T-tube removal, and occur at the T-tube insertion site. Bile leaks may complicate up to 33% of all T-tube removals, depending on the diagnostic criteria used [41–44]. The incidence of late bile duct leaks was reported to be 7%, with a mean time to presentation of 118 days after transplantation despite prolonged T-tube placement [37]. Early T-tube insertion site leaks may reflect relative downstream obstruction or papillary dysfunction (Fig. 1). They usually respond to unclamping of the T-tube, placement of a percutaneous transhepatic cholangiography-guided drainage (PTCD), Yamakawa-drainage (Fig. 2), or endoscopic sphincterotomy, or stenting [45]. The incidence may be lowered by tunneling the T-drain through the mesocolon on its way outside the abdominal cavity, as performed in our center. Other centers have proposed a modified technique of T-tube removal, using the T-tube itself as a counter-drain under fluoroscopy guidance [46]. An impact of T-tube removal earlier than the usual period of 6 weeks to 3 months after OLT has not yet been confirmed [43].

Because of these data, the insertion of a T-tube is still discussed controversially. Two prospective, randomized trials examined the impact of T-tube use after OLT. In

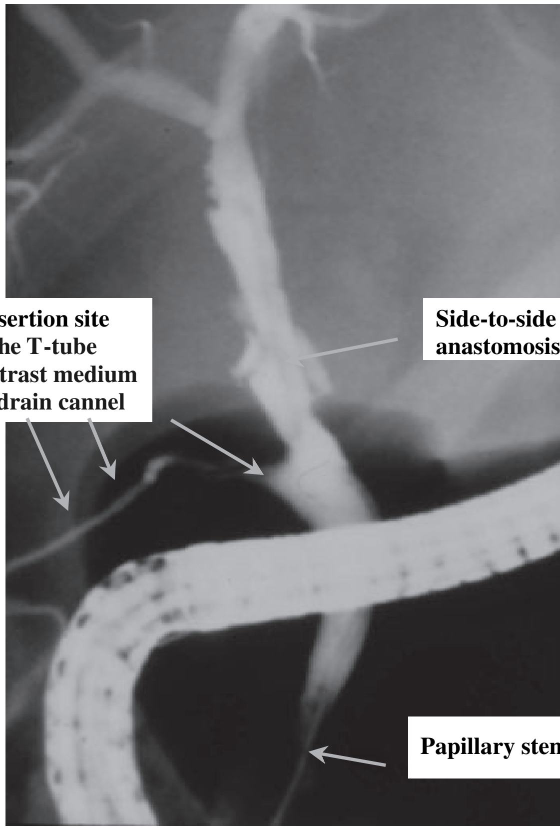

Figure 1 Leak of the T-tube insertion site after deceased donor full size orthotopic liver transplantation using a side-to-side bile duct anastomosis and T-tube. Ampullary dysfunction most probably contributed to the leakage by increasing the intraductal pressure. The illustration shows a leak of the T-tube insertion site after removal of the T-tube with traces of contrast medium along the former drain cannel.

one study, only one stricture was seen in the 30 patients receiving CC with a T-tube; however, six of 30 patients (20%) who had CC without a T-tube developed strictures and three eventually required conversion to choledochojejunostomy (CJ) [47]. The largest prospective randomized study compared 90 patients with or without T-tube. The authors found a significant increase in biliary complications in the T-tube group (33%) as compared with patients transplanted without T-tube (15.5%). In the T-tube group, 60% of complications were related to the T-tube, with cholangitis being the most prominent complication [48]. Additionally, Shimoda *et al.* [49] performed an analysis of cost-effectiveness regarding the use of T-tubes in OLT. The application of T-tubes resulted in significantly higher complication rates (32.9% vs. 15.5% without T-tube); however, complication related costs were not significantly higher.

Late bile leaks are infrequent events. They are sometimes caused by recurrence or persistence of early complications or can be due to delayed removal of T-tubes, transhepatic anastomotic stents or biliary stent migration and perforation. Leakages secondary to late HAT were also reported and correlated significantly with donor age [50].

Generally speaking, biliary leakage from any source can be serious; however, leaks from the anastomosis are the most hazardous. A rare, but grave complication in the early postoperative period is diffuse biliary necrosis secondary to acute arterial thrombosis or blood group incompatibility between donor and recipient. The presentation is usually a combination of massive bile leakage, sepsis, cholestasis, and associated complications such as pleural effusion.

Treatment

Anastomotic leakages, particularly in the case of duct-to-duct anastomosis, can be successfully managed without surgery if they are small and localized. If a T-tube was used, they can be managed conservatively by leaving the T-tube open to divert bile flow. A repeat cholangiogram in 1–2 weeks eventually confirms healing of the bile duct. Endoscopic or percutaneous stenting can resolve minor leaks in the absence of significant right upper quadrant or systemic sepsis. However, if the anastomosis is seriously disrupted or biliary extravasation is major, re-operation with revision is the safest approach [32,51]. A therapeutic PTC approach to Roux-en-Y CJ anastomotic leaks with placement of an internal–external drain accompanied by percutaneous drainage of fluid collections, biloma or abscesses, is recommendable [52]. However, in many cases, operative management with primary repair or

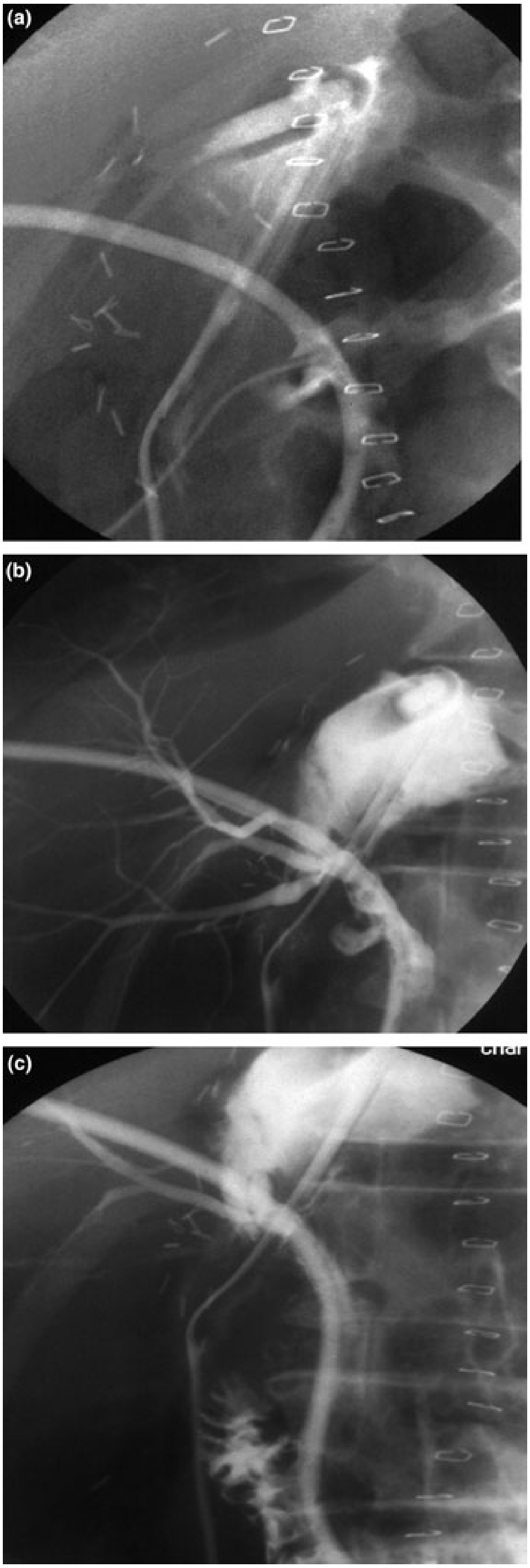

Figure 2 (a) Leak at the T-tube insertion site after right lobe living donor liver transplantation (LD-LTx). A yamakawa-drain has already been placed with the T-tube still *in situ*; there is a collection of contrast medium cranially to the leakage site which is drained by an easy flow drainage and an additional foley catheter. (b) The T-drain has been removed and the leakage is still depicted. (c) After replacing of the yamakawa drain, the leakage is closed.

refashioning of the anastomosis is required after intra-abdominal infection has resolved [3,33,53].

Leaks at the T-tube insertion site may be treated conservatively and symptomatically over a limited period of time [1]. One third to half of such leaks were reported to close spontaneously within 24 h [42,43]. Further intervention is indicated, if signs and symptoms persist. Recommended approaches comprise conservative, endoscopic, and surgical treatment [54]. It has been shown that in most cases nonsurgical management is effective (Fig. 2) [32]. Biliary tract stenting with or without endoscopic sphincterotomy as well as percutaneous treatment (Fig. 2) can be applied successfully in over 90% of biliary tract leaks [32,37,55]. Endoscopic sphincterotomy alone has also been reported to be effective in treating post-OLT bile leaks as ampullary dysfunction sometimes contributes (Fig. 1). Some centers advocate endoscopic placement of nasobiliary catheters proximal to the leak [41], which was reported to ensure closure of bile leak in almost all patients within 14 days [56,57]. Recurrent leaks were demonstrated to be less frequent with the use of nasobiliary drainage as compared with biliary stents [58]. Some centers prefer to use internal plastic stents, which are placed by endoscopy and remain in place for 2 weeks [32] to several months [59] prior to removal.

Nonanastomotic leakages are preferably treated by endoscopic retrograde cholangiography (ERC) or PTC with stenting of the bile leak using plastic internal stents. The advocated intervals until re-ERC/PTC and stent-removal range from 4 weeks to 3 months [1,3,33,59].

Cut surface leaks may be located and treated by ERC and sphincterotomy, thus reducing the intraductal pressure. When occurring in recipients with bilioenteric anastomosis, such as in reduced size OLT or LD-LTx, percutaneous drainage using a PTCD or a Yamakawa-drainage may be necessary. Associated biloma can be treated by percutaneous sonography- or CT-guided drainages [52,53]. Surgical therapy as definitive treatment may be necessary for massive bile leaks if conservative treatment fails. However, reducing intraductal pressure should precede surgical treatment of cut surface leaks in order to avoid frustraneous surgery.

Late bile leaks usually resolve spontaneously. If symptoms persist, endoscopic management is the therapy of choice to proceed with [33]. However, they are particularly difficult to treat when HAT contributed to the etiology. Late bilary leaks may be accompanied by strictures because of chronic inflammatory reactions in the surrounding tissue, finally necessitating surgical intervention. Despite recurrent cholangitis and cholestasis secondary to ischemic injury of the biliary tree, synthetic graft function may be preserved for a prolonged period. Hence, nondefinitive, temporary measures may often be considered until definitive treatment by retransplantation is necessary.

In general, surgical intervention is required if conservative management fails, and if the anastomosis is seriously disrupted or biliary extravasation is major, and often when there is evidence of HAT. Conversion to a bilioenteric anastomosis, which allows for wide debridement of necrotic and infected tissue, is advocated when periductal infection makes direct re-institution of duct-to-duct anstomosis impossible [3,60]. Primary repair of duct-to-duct anastomotic leaks have been reported in technically ideal situations [51].

Bile collection/biliary abscesses

Undetected or clinically inapparent bilomas may be the origin of serious and insidious complications, such as bacterial super infection by ascending pathogens potentially leading to intraabdominal abscesses and sepsis. One of the most feared secondary complication is massive and often deleterious arrosion bleeding of the hepatic artery.

The ERC plays a diagnostic and therapeutic role by defining and eventually treating the underlying leakage [1–3,61]. Use of sonography- or CT-guided indwelling catheters is adequate and sufficient in most cases to drain sterile or superinfected bilomas [52]. This should be, if necessary, accompanied by antibiotic and further symptomatic therapy. Intrahepatic bile leaks communicating with the biliary system may resolve spontaneously or may respond adequately to sphincterotomy. Surgical repair of the biliary tree is required in the case of insufficient endoscopic therapy of the underlying biliary leakage or secondary complications.

Biliary strictures

Incidence and etiology

Bile duct strictures are the most frequent cause of delayed biliary complications and usually occur later than bile leaks [4,37]. Later appearing strictures are often the result of vascular insufficiency and fibrotic healing, whereas early anastomotic strictures are mainly because of technical error [1,3,33]. Biliary strictures complicate approximately 3–14% of all OLTs performed [1,4,53,54] and account for up to 40% of all biliary complications. It is useful to classify strictures as anastomotic (Fig. 3) and nonanastomotic (Figs 4–6). The latter are subclassified as hilar (Fig. 4) or intrahepatic (Figs 5 and 6) reflecting differences in etiology and responses to treatment.

Three prospective trials on the usefulness of T-tubes did not support the hypothesis that patients without T-tubes are at higher risk for stricture formation [40,48,50]. Biliary strictures can occur with either type of biliary reconstruction. At least two large series reported strictures to be more common with Roux-en-Y CJ reconstruction [4,42]. Because of the direct bilioenteric connection, signs and symptoms of cholangitis may be more common at presentation. The incidence of late anastomotic strictures may increase in the future as more complex biliary reconstructions of often two or more small-caliber bile ducts are necessary in split-liver and LD-LTx [24,25,62].

Nonanastomotic strictures are frequently hilar in location, but may be diffusely intrahepatic. These strictures are often complex and in multiple locations and may be associated with the formation of biliary casts or stones. Approximately 50% of patients who present with nonanastomotic strictures have HAT [1,63,64]. In 2–20% of patients, pathologic changes of the biliary tree develop which are localized proximal to the anastomotic site and occur in the presence of an obviously normal vascular situation [36,65–68]. Because they resemble the biliary tract changes observed in cases of ischemic biliary damage [28] they have been referred to as ischemic-type biliary complications or lesions (ITBL) [65,66]. They are subclassified as intrahepatic, or extrahepatic (Fig. 4), or both intra- and extrahepatic ITBL (Figs 5 and 6) [59].

The appearance of these lesions suggests that microcirculatory problems because of ischemia–reperfusion injury may play a role in their development, but their exact pathogenesis remains speculative. An increased frequency of such lesions has been described in patients with prolonged cold ischemic times [28,36,65] or with delayed re-arterialization of the graft. The injury may be a direct effect of cold ischemia on the biliary epithelium or damage to the biliary tree microvasculature [69].

The main role of microcirculatory impairment is supported by a recent study hypothesizing that insufficient perfusion of biliary arterial vessels might be responsible for the ITBL phenomenon. Additional arterial backtable pressure perfusion of 59 grafts lowered the ITBL rate significantly in comparison with the standard procedure ($n = 131$). Within the first 3 days peak aspartate aminotransferase and alanine aminotransferase levels were significantly lower in the arterial perfusion group. The authors advocated additional arterial backtable perfusion as the standard technique in liver procurement [70]. Additionally, multivariate analysis identified donor age as determinant of the incidence of ITBL. However, further factors, such as chronic ductopenic rejection [71],

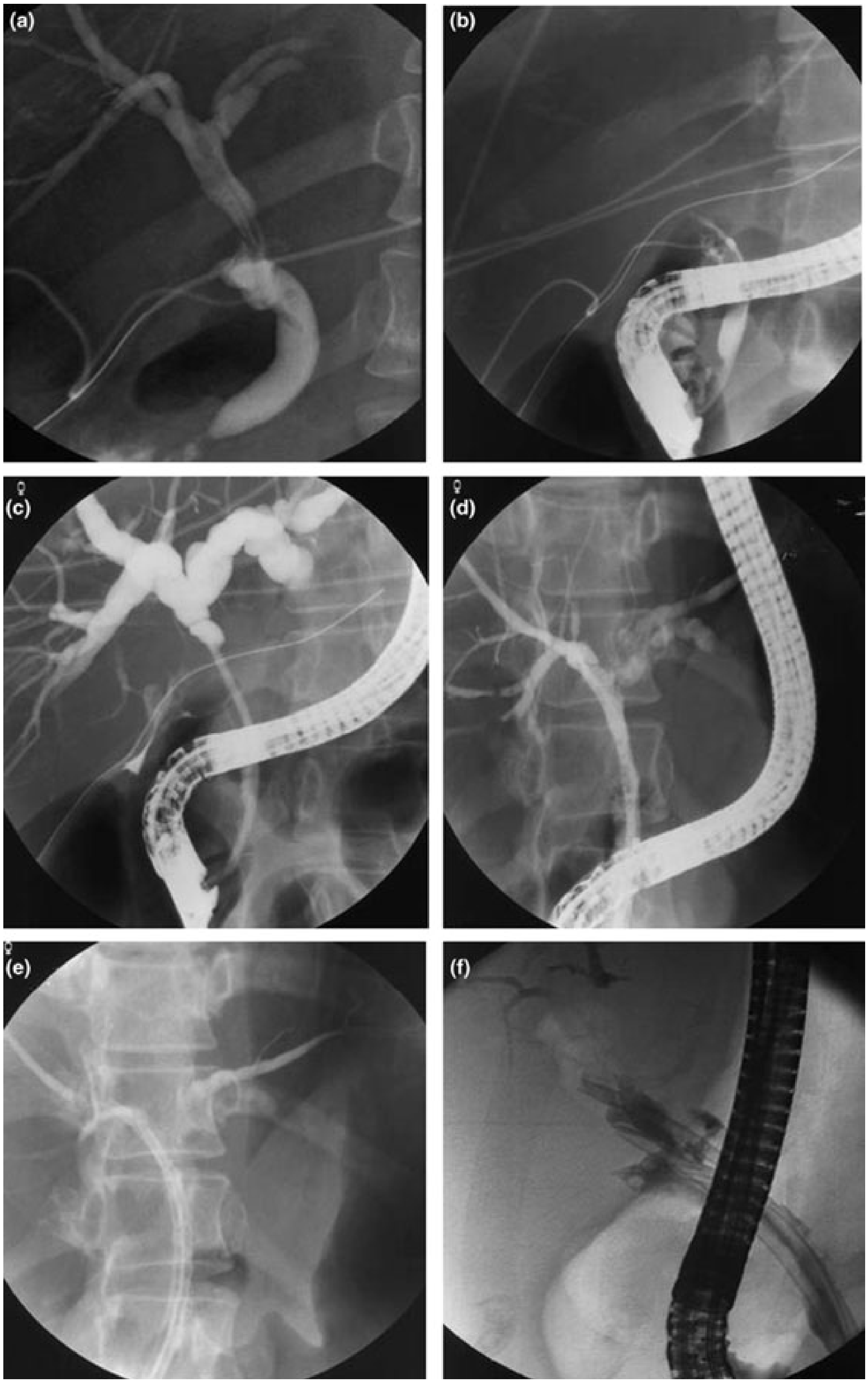

Figure 3 (a) Early anastomotic stricture, diagnosed by the application of contrast medium via the inserted T-tube. (b) Endoscopic retrograde cholangiography (ERC) imaging of the recipient bile duct with localization of the anastomotic stricture and ERC-guided insertion of a guidewire. (c) After removal of the T-tube and balloon dilation of the stricture, an internal stent is placed. Filling of the biliary tree with contrast medium shows dilation of the intrahepatic bile ducts. (d) Effective release of contrast medium through the inserted internal stent. (e) 3 months after insertion of the first stent, a further dilation is performed and a second internal stent placed. (f) Triple stenting 6 months after orthotopic liver transplantation as final step of a prolonged multi-stenting approach to provide a persistent therapeutical success in a case of early anastomotic stricturing.

Figure 4 Nonanastomotic, hilar stricture as an example for an ischemic type biliary lesion.

concomitant CMV infection, and ABO blood type mismatched grafts were identified [72,73]. Finally, several studies provided convincing evidence that a primary sclerosing cholangitis can recur after OLT [74]. An incidence of 5–20% and an interval for diagnosis of at least 1 year after OLT, resulting in predominantly intrahepatic, nonanastomotic strictures, were reported [74–76].

Diagnosis

Often, asymptomatic elevation of serum chemical markers is the first sign of biliary complications prompting initiation of further examinations. The appropriate diagnostic workup has been repeatedly reviewed in an attempt to reach the most accurate strategy [77–79]. Transabdominal ultrasonography (TAUS) as noninvasive imaging method is often the first step. However, TAUS cannot be considered reliable for the early detection of biliary complications, as it lacks sufficient sensitivity to detect small but clinically important obstructions, generalized ductal changes, and leaks [80]. Having a certain variability of experience with TAUS, a cautious approach seems advisory, suggesting that the absence of bile duct dilation on sonography should not preclude further evaluation in clinically suspicious cases [44,81,82]. A more definitive assessment of biliary complications can be made by means of direct cholangiography via T-tube, PTC and ERC, which can also be used as an access for therapeutic purposes [79,81,83]. Cholangiography is considered the gold standard and accepted as the most effective and accurate method for identifying early post-transplant

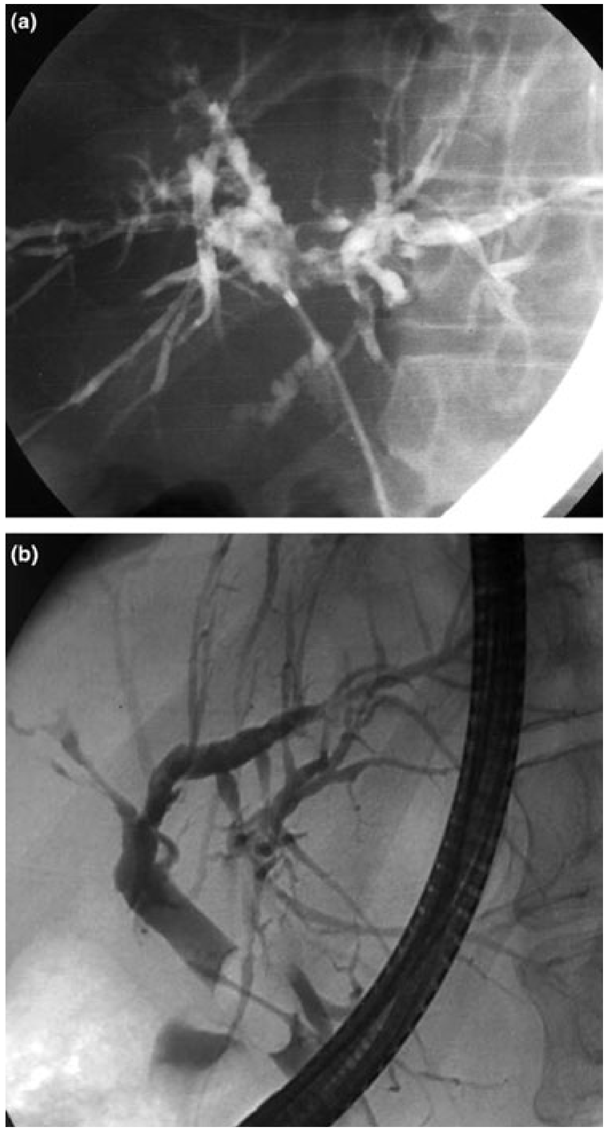

Figure 5 (a) Advanced form of ischemic type biliary lesion with gross destruction of intrahepatic bile ducts and hilus approximately 3 months after orthotopic liver transplantation (OLT). As depicted, endoscopic retrograde cholangiography (ERC) is performed for diagnostic reasons and subsequent intervention. (b) Identical patient 2 years after OLT having undergone several ERC-sessions with recurrent dilations, extraction of debris and long-term stenting. Wide areas of the biliary tract have consolidated thus avoiding a further decline of liver function and re-OLT.

biliary complications [84,85]. In the absence of a T-tube, visualization of the biliary system is only possible when invasive procedures such as PTC and ERC are used, which are themselves associated with complications in 3.4% of PTC and 7% of ERC procedures [26]. In patients with bilioenteric anastomosis, PTC is generally required for minimal invasive therapeutic intervention. Routine

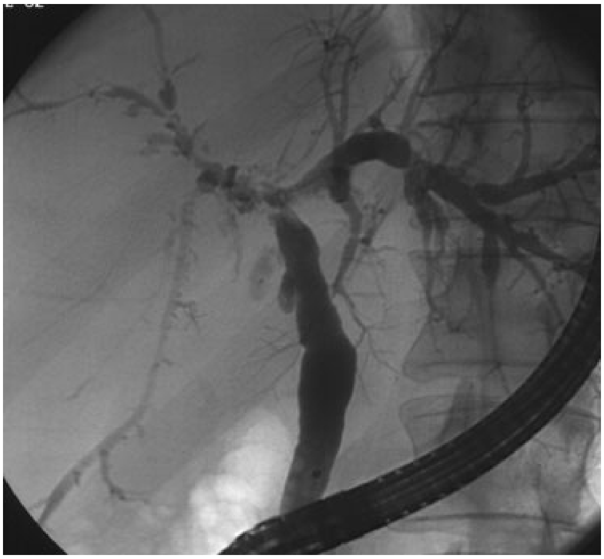

Figure 6 Example for mutiple predominantly right-sided, nonanastomotic, hilar and intrahepatic strictures in the course of an ischemic type biliary lesion approximately 1 year after deceased donor orthotopic liver transplantation.

use of ERC in asymptomatic patients after OLT with abnormal liver enzymes was not found to be useful, because a low sensitivity in predicting the overall risk for biliary complications was reported [86]. Sensitivity, specificity, and positive and negative predictive values for successful ERC in detecting early biliary complications in patients with unsplinted CC were reported to be 80%, 98%, 89%, and 97%, respectively, whereas those for predicting the overall rate of biliary complications were respectively 53%, 98%, 89%, and 89%.

Besides the current diagnostic standard, i.e. computed tomography, for a wide range of complications after OLT, MRC has recently been proposed as a reliable noninvasive screening method in patients with biliary complications after OLT [87–89]. MRC was successfully used for anatomic and morphologic analysis of the biliary tract in living related pediatric OLTs, preceding interventional or surgical treatment of biliary complications [90]. Additionally, MRC may be a useful noninvasive diagnostic tool for the follow-up of liver transplant patients [23,91–93]. It has also been proven to be useful in detecting bile leaks. However, formal comparative studies with other imaging modalities have not yet been published [21,94]. As the biliary tract is inaccessible by ERC in patients with bilioenteric anstomosis, MRC would appear particularly attractive in these patients [95]. Boraschi *et al.* [26] prospectively compared MRC versus ERC and clinical history in 113 liver transplant patients with suspected biliary complications. Sensitivity and specificity were >90%, and the positive predictive value was reported to be 86%. MRC was thus suggested to be a feasible imaging modality for biliary tract evaluation when there is low or unspecific suspicion of biliary tract disease or when ERC and PTC are unsuccessful. Additionally, a comprehensive assessment of concomitant vascular, parenchymal, and extrahepatic complications was described [96]. However, three main restrictions were defined: MRC tends to overestimate biliary strictures at the anastomotic site, MRC cannot usually distinguish circumscribed perianastomotic ascitic fluid from biloma, and the precision of its measurement of the length of nonanastomotic strictures, particularly those involving the hepatic bifurcation and right or left hepatic ducts is restricted.

Treatment

Anastomotic strictures. While early experience with endoscopic therapy for anastomotic strictures revealed a significant rate of failures requiring surgical intervention [33,97], more recent studies support the primacy of ERC and percutaneous treatment by PTC with either stenting or dilation [2,57,64,98,99]. Reports indicate long-term success in more than 70% of patients [97,98,100]. Up to 75% of patients diagnosed with anastomotic strictures were shown to be stent-free 18 months after initial ERC [1], using the combination of endoscopic balloon dilation and stenting of anastomotic strictures (Fig. 3). However, as relapse rates of 30–40% were reported, there is a concern about the long-term effect of balloon dilation and temporary stent placement for late-appearing anastomotic strictures (usually after 3 months) [59,101]. Several reports stressed the necessity of long-term endoscopic stenting of anastomotic strictures with intercurrent endoscopic re-assessment [68]. In selected cases, double or triple parallel stenting may be successful. (Fig. 3) With these treatment modalities, patient and graft survival rates similar to the ones of an uncomplicated control population after OLT were achieved.

Surgical revision and creation of a Roux-en-Y CJ is indicated when endoscopic or percutaneous treatment failed [1,3,37,60,68]. In some cases re-establishment of a CC is possible. Percutaneous transhepatic balloon dilation of anastomotic strictures has been shown in one study to have a 66% long-term success rate and is of special importance for the initial management of strictures affecting choledochojejunostomies [1,3,68]. Some centers prefer to leave percutaneous biliary drains across the stricture, maintaining the patency of the anastomosis and allowing easy access to the stricture for repeated treatment [37]. Self-expanding metal stents have also been used in some centers [101,102]. They have been discussed controversially because of the high rate of stent occlusion and the obvious difficulties in the case of surgical conversion to

CJ [102]. Persistent Roux-en-Y CJ strictures often require surgical revision.

Nonanastomotic strictures. Nonanastomotic strictures are commonly classified as having less favorable prognosis and being less responding to conservative endoscopic or interventional therapy [3] than anastomotic strictures. Strictures that appear within the first 3 months were shown to be more amenable to endoscopic measures than those that developed later (Figs 4–6). A recent study of dilation and stenting of hilar and intrahepatic strictures achieved a success rate of only 28.6% compared with a 75% success rate with anastomotic strictures [64]. Despite this dismal outcome, nonanastomotic strictures have primarily been treated using interventional endoscopic or transhepatic techniques [36,65,59]. However, frequent re-interventions and long-term antibiotic treatment are required in many patients when compared with patients having anastomotic strictures. Moreover, patients have a higher prevalence of concomitant choledocholithiasis and biliary casts, and successful endoscopic therapy takes longer [1]. In selected cases, double or triple parallel stenting may be successful.

There are no randomized controlled trials comparing the risk/benefit ratio of the different endoscopic or percutaneous techniques. Both, PTC and ERC, are associated with characteristic limitations and risks. Anastomotic and nonanastomotic strictures after creation of a bilioenteric anastomosis are only accessible by PTC. Because the rate of reduced-size OLT and complex biliary reconstructions in LD-LTx is increasing, percutaneous treatment options will gain even more importance in the future. Their use is limited in patients with impaired liver function and thereby increased risk of bleeding complications. ERC provides direct access to the biliary system without invasive measures, provides direct access to ampullary dysfunction by treatment with sphincterotomy, however, is associated with a relevant risk of pancreatitis. Additionally, ERC cannot be used in recipients with bilioenteric anastomosis. PTC and ERC were reported to be associated with overall complication rates in 3.4% of PTC and 7% of ERC procedures [26]. Recommendations regarding the use of both procedures often do not reflect scientific evidence, but rather individual experience and center policy. Early reports suggested that despite attempts at nonsurgical intervention, 25–50% of patients with nonanastomotic strictures die or undergo retransplantation for these complications [36,42,65]. Advances in endoscopic and percutaneous therapy of biliary strictures have improved these outcomes so that the overall patient survival does not differ from transplant recipients without stricture [64,65] as long as the indication for surgical reconstruction or retransplantation occurs in a timely fashion. Particularly patients with suspected recurrence of primary sclerosing cholangitis should be considered for retransplantation in due time.

A recent report by Schlitt *et al* [68]. evaluated the feasibility, complication rate, and results of a reconstructive surgical approach that included resection of the hepatic bifurcation for the treatment of patients with hilar ITBL (Fig. 4) unrelated to vascular problems after OLT. All patients treated in this study either already had several endoscopic interventions or the biliary tree could not be approached adequately either after primary hepaticojejunostomy or because of extensive stenosis. Surgical reconstruction in 14 patients was accomplished by resection of the bifurcation and hepatojejunostomy. Clinical symptoms and biochemical parameters normalized or improved considerably in 88%. In three patients with more extensive biliary destruction, portoenterostomy with or without peripheral hepatojejunostomy was performed. Only one patient who underwent an additional peripheral hepatojejunostomy showed a considerable improvement for about 18 months. The other two patients required rapid retransplantation.

It may be concluded that the reconstructive surgical approach should be reserved to patients not responsive to repeat endoscopical interventions, with recurrent cholangitis, or those with restricted accessibility of the biliary tract by percutaneous or endoscopic methods. Because of the restricted availability of donor organs and the increased risk of a retransplantation, the option of retransplantation should be reserved for patients in whom no adequate surgical reconstruction can be accomplished. The latter group of patients comprise those suffering from intrahepatic ITBL not responding adequately to endoscopic or percutaneous therapy or not suitable for surgical reconstruction, patients with recurrent cholangitis resistant to conservative treatment, patients with frustraneous surgical reconstruction, and patients with progredient ITBL-associated cholestasis and liver insufficiency.

Outside of endoscopic therapy, there is little medical or dietary management that can be applied for post-OLT biliary complications. Medical treatment for intrahepatic strictures comprises ursodeoxycholic acid (UDCA) and antibiotics for stricture-induced cholangitis. There are no data proving benefitial effects of antibiotic prophylaxis. UDCA has often been used as a neoadjuvant to endoscopic retrograde cholangiopancreatography (ERCP) or supportive therapy in the setting of nonanastomotic stricture formation, common bile duct stones, and casts. UDCA and low fat diets may be recommended in this setting, but no large, randomized trials have advocated medical or conservative management alone [103] or even analyzed the impact of supportive UDCA treatment. However, in selected patient populations, such as recipients with PSC, UDCA may be advocated for other reasons: patients with PSC are at greater risk of colonic cancer, which may be reduced by UDCA[104]. Recent diagnosis of PSC and no UDCA treatment were predictors of malignancy after OLT [105].

Ampullary dysfunction

Approximately 2–5% of all liver-transplanted patients develop a significant dilation of the bile duct in association with biochemical abnormalities in the absence of cholangiographic evidence of obstruction [1,4,63,66] and clinical symptoms [106]. A mild dilation is quite commonly observed, but usually not clinically relevant. This clinical entity is referred to as papillary dyskinesia or ampullary and sphincter of Oddi dysfunction. It has been hypothesized that operative denervation of the sphincter of Oddi [106] causes an impaired ampullary relaxation. The average time to onset was reported to be 35 weeks, however early onset may occur only several days after OLT. The diagnosis may be confirmed clinically by improving biochemical parameters, i.e. cholestosis parameters in particular, after T-tube unclamping, and by delayed drainage of contrast medium after cholangiography. Ampullary dysfunction may trigger biliary leakages by increasing the intraductal preasure upstream (Fig. 1). ERCP shows the typical sign of biliopancreatic reflux of contrast medium.

As bile duct pressure (and presumably sphincter of Oddi pressure) decreases to normal values by 3–4 months after OLT, endoscopic treatment in terms of transpapillary stenting or endoscopic sphincterotomy should be considered as initial approach [2,3,68,106,107]. It replaced the traditional approach of CJ which should be reserved for patients with ampullary dysfunction resistant to endoscopic sphincterotomy [4].

Biliary stones, sludge, and casts

Biliary stones and sludge predominantly occur later than 3 months after OLT. Biliary sludge is commonly associated with either anastomotic or nonanastomotic biliary strictures. They may be seen in up to 90% of patients with bile stones [108,109]. Occassionally, an aggregation of extensive casts ('staghorn calculus') has been described [1]. Additionally, infection, foreign bodies (T-tube, stents), mucosal damage, kinking of the bile duct, ischemia, cholesterol supersaturation of the bile acid, calcineurin inhibitors, and depletion of the bile acid pool, because of external drainage via T-tube, have been discussed as further etiologies [109,110].

Endoscopic sphincterotomy and stone extraction were reported to be successful in 88–91% of patients [1,2]. Endoscopic extraction may also be tried for biliary casts, but even repeated interventions usually do not result in complete and permanent clearance of the biliary tree. For casts that are particularly difficult to extract, surgical extraction, conversion to Roux-en-Y CJ or retransplantation may be required [2]. As stated before, UDCA and low fat diets may be recommended in this setting, but no large, randomized trials have advocated medical or conservative management alone [103].

Complications related to bilioenteric anastomosis

Choledochojejunostomy is a relatively rare type of biliary drainage in deceased donor full size OLT and preferred in recipients suffering from primary or secondary biliary tract disease (primary and secondary sclerosing cholangitis, cholangiocarcinoma, biliary atresia). Additionally, the Roux-en-Y CJ is frequently used as biliary drainage during retransplantations, with size disparities between donor and recipient ducts, reduced-size grafts, when a critical blood supply to the distal donor bile duct is foreseeable [37], for surgical treatment of biliary strictures not adequately treated by endoscopic means [68], and in pediatric liver transplant patients. It has gained importance for living donor liver transplantion and split OLT, as complex reconstruction of several small bile ducts has to be performed primarily or secondarily [30,62]. Problems related to the Roux-en-Y CJ include increased surgical time, stricture or leakage of the CJ, bowel ischemia, perforation, Roux limb torsion, enteric anastomotic bleeding, delayed mixing of bile with intestinal contents, altered cyclosporine absorption, blind loop syndrome, and biliary colonization/infection from intestinal microbial reflux [111,112]. In addition, creation of CJ restricts endoscopic evaluation of the biliary system, occasionally requiring a PTC. As MRC has emerged as a sensitive, noninvasive diagnostic tool, CJ-related diagnostic problems are likely to decrease.

Treatment of CJ-related complications may be performed transcutaneously in the case of strictures or leakages. However, the rate of conversions to surgical revision is higher than with CC. Significant bleeding or leakage and Roux limb torsion do almost generally require surgical intervention.

Hemobilia

Hemobilia is a rare complication (approximately 0.1%) after OLT. It is usually related to percutaneous liver biopsy or PTC [1,113–115]. Massive transpapillary gastrointestinal bleeding, formation of clots, and biliary obstructions are the most prominent potential immediate consequences. Facultative clinical symptoms may be right upper quadrant pain and jaundice [113]. Multiple intrahepatic stones above the level of obstruction were reported occasionally [114]. Hemostasis is often achieved spontaneously. Treatment of hemobilia and associated biliary obstruction may occasionally require both hemostasis and treatment of the biliary obstruction. Angiographic embolization of hepatic artery pseudoaneurysms is indicated for hemostasis [1]. Biliary obstruction can be managed with percutaneous drainage, endoscopic thrombus extraction, and in unusual cases, surgical intervention [113,114].

Mucocele

Mucoceles are rare complications caused by defective drainage of mucus produced by the lining cells of the cystic duct remnant into the bile duct [32], eventually leading to extraluminal compression of the common duct. Therapy of choice is surgical excision or drainage of the cystic duct remnant by enteric anastomosis [37].

Conclusion

The spectrum of biliary complications has changed over the past decade as a result of the establishment of split liver, reduced-size, and living donor liver transplantation. Apart from technical developments, novel diagnostic methods have been introduced and evaluated in OLT, the most prominent being magnetic resonance imaging (MRI). Treatment modalities have also changed over the past years towards a primarily nonoperative, endoscopy-based strategy, leaving the surgical intervention for lesions which otherwise are not curable. The management of biliary complications after OLT requires a multidisciplinary approach. Conservative, interventional, or endoscopic treatment options have to be weighed up against surgical re-intervention. Whereas T-tube related leaks are a precedent for endoscopic treatment [2], complex hilar or intraheptic strictures because of ITBL may be treated temporarily or long-term by ERC/PTC and stenting [59], but finally require surgical repair using a Roux-en-Y CJ [68] with excellent 5-year survival rates of 71% [116] or even retransplantation. However, early and large anastomotic leakages are in many centers indications for immediate re-operation [1,3,68].

Generally speaking, endoscopic treatment has gained an increasing role in the treatment of biliary complications after OLT. Our experience clearly demonstrated that a majority of complications could be resolved by endoscopic treatment [59]. In many cases, diagnostic ERC or PTC may be followed immediately by therapeutic measures aiming definitive restorage of bile flow in the biliary tract by balloon dilation of strictures and removal of debris and stones. They may thus provide curative treatment, or ease the patient's complaints, or bridge the time until decision of definitive treatment. However, an essential guideline in the use of ERC is to recognize its limitations. Particularly in the patient with diffuse intrahepatic strictures and underlying HAT, the goals of endoscopic therapy must be clearly delineated prior to the procedure. Routine use of ERC in asymptomatic patients after OLT with abnormal liver enzymes was not found to be useful. Sensitivity, specificity, and positive and negative predictive values for successful ERC in detecting early biliary complications in patients with unsplinted CC were reported to be 80%, 98%, 89%, and 97%, respectively whereas those for predicting the overall rate of biliary complications were respectively 53%, 98%, 89%, and 89%. Although highly specific and moderately sensitive in detecting early biliary complications, routinely performed ERC has been shown to have low sensitivity in predicting the overall risk for biliary complications [86].

With longitudinal follow-up and continued improvement in the survival of liver transplant patients, more complete data on the long-term consequences of biliary complications and the long-term efficacy of endoscopic therapy will become available.

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