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# Role of Interventional Radiology in the Treatment of Biliary Strictures Following Orthotopic Liver Transplantation

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## Abstract

*Purpose:* To evaluate the efficacy and safety of percutaneous treatment of biliary strictures complicating orthotopic liver transplantation (OLT).
*Methods:* Between October 1990 and May 2000, 619 patients underwent 678 liver transplants. Seventy of the 619 (11%) patients were found to be affected by biliary strictures by July 2000. Bilioplasty was performed in 51 of these 70 (73%) patients. A cohort of 33 of 51 (65%) patients were clinically followed for more than 12 months after the last percutaneous treatment and included in the survey results.
*Results:* After one to three treatments 24 of 33 (73%) patients were stricture-free on ultrasound and MR cholangiography follow-up. A delayed stricture recurrence required a fourth percutaneous bilioplasty in two of 33 (6%) patients. A surgical bilioenteric anastomosis was performed in six of 33 (18%) patients. Retransplantation was performed due to ischemic damage in one of 33 (3%) patients.
*Conclusion:* Interventional radiology is an effective therapeutic alternative for the treatment of most biliary strictures complicating OLT. It has a high success rate and should be considered before surgical interventions. Elective surgery may be necessary in a few failed cases or those with more severe and extensive biliary strictures.

**Key words:** Liver, transplantation—Bile ducts, stenosis or obstruction—Bile ducts, interventional procedure—Bile ducts, calculi

Orthotopic liver transplantation (OLT) is a widely accepted treatment for end-stage liver diseases. Despite improvements in organ preservation technology, refinements in procurement and surgical techniques, and advances in immunosuppressive strategies, biliary tract complications remain a significant cause of morbidity and mortality after OLT [1].

In major transplant centers the incidence of biliary complications has been reported to vary from 10% to 26%. Complications are mainly due to biliary strictures (at anastomotic or nonanastomotic sites), stones, sludge and biliary fistulae [1–5]. Less frequent biliary tract complications are intrahepatic fluid collections and abscesses [6, 7].

Early diagnosis and treatment of biliary tract abnormalities may increase survival rate after liver transplantation [1]. Complicated surgical reintervention has to date been the initial mainstay of therapy. Percutaneous treatment has also been considered an alternative [3–5] and is better accepted by this population of patients, who have undergone prolonged pharmacologic and surgical therapy pre- and post-OLT [1]. Moreover, in the last few years interventional radiological techniques have made significant progress [8].

In this report we present our 9-year experience of percutaneous treatment of biliary strictures complicating liver transplantation and discuss the validity of the latter therapeutic approach.

## Materials and Methods

Between October 1990 and May 2000, 619 patients underwent 678 liver transplants in our institution. The indications for liver transplantation are summarized in Table 1.

End-to-end choledocho-choledochostomy (C-C) with insertion of a T-tube to splint the biliary anastomosis was used in 563 (83%) cases. A choledocho-jejunostomy with a Roux-en-Y loop (CR-Y) was performed during the transplant or following surgical revision of the anastomosis in 115 (17%) cases. Ex vivo split liver transplantation was done in 11 of 619 patients.

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**Table 1.** Indications for liver transplantation (pre-OLT diseases) and rate of biliary strictures in relation to pre-OLT hepatic diseases

| Pre-OLT diseases | No. of OLT | No. of biliary strictures | % biliary strictures/ no. of OLT |
|---|---|---|---|
| PHCC | 269 | 27 | 10% |
| PHBC | 153 | 23 | 15% |
| PHBC+ PHCC | 34 | 7 | 20% |
| *Total post-hepatic cirrhoses* | *456* | *57* | *12%* |
| ALC | 66 | 6 | 9% |
| PBC | 21 | 0 | 0% |
| SCC | 19 | 3 | 16% |
| MED | 9 | 1 | 11% |
| WID | 8 | 0 | 0% |
| FUH | 20 | 0 | 0% |
| UKC | 20 | 3 | 15% |
| Total cases | 619 | 70 | 11% |

PHCC, post-hepatic C cirrhosis; PHBC, post-hepatic B cirrhosis; ALC, alcoholic cirrhosis; PBC, primary biliary cirrhosis; SCC, sclerosing cholangitis; MED, metabolic disease; WID, Wilson disease; FUH, fulminant or subacute hepatitis; UKC, cirrhosis, unknown cause

Abdominal ultrasound (US) with Doppler scanning was used to confirm hepatic artery patency in all transplanted patients. Poor systolic or diastolic flow and complicated hepatic arterial sampling were interpreted as abnormal Doppler findings.

Transplanted patients with fever, jaundice, nausea and/or abdominal pain underwent laboratory examination. If elevated cholestatic enzyme levels were detected US, CT, MR cholangiography and T-tube cholangiography were performed, and 70 of 619 (11%) patients were found to be affected by biliary tract strictures (data up to July 2000).

### *Exclusion Criteria*

Eleven of 70 (16%) patients affected by biliary complications were not included in this study: eight had severe and extensive biliary strictures treated immediately by surgery; one had a hepatic artery stenosis, thought to be responsible for the biliary complication, which was percutaneously stented. Multiple biliary abscesses with sludge and strictures were assessed before death in two patients.

No treatment was performed in eight of 70 (11%) cases with mild biliary stenoses in asymptomatic patients or those with normal serum enzymes.

### *Biliary Strictures*

This study included 51 patients (37 men, 14 women; age range 32–66 years, mean age 48.9 years) with biliary strictures complicating OLT. Thirty-seven patients had C-C anastomosis, 14 had CR-Y anastomosis.

Biliary stricture site was at the anastomotic level only in 38 of 51 (74%) patients (30 CC, 8 CR-Y); 10 of 51 (20%) patients had anastomotic stenoses associated with intrahepatic strictures (6 CC, 4 CR-Y) and three of 51 (6%) patients had nonanastomotic intrahepatic stenoses only (1 CC, 2 CR-Y).

Strictures occurred within 3 months of OLT in 19 (37%) patients and in another 22 (43%) patients within 12 months. Biliary symptomatology occurred in eight patients within the second year following OLT and in two further patients at 48 and 52 months, respectively.

Biliary stenosis, lithiasis and/or sludge within the biliary tree was found in 21 of 51 (41%) of the patients.

### *Biliary Stricture Treatment*

All 51 patients were percutaneously treated after local anesthesia (lidocaine 2%; Angelini, Roma, Italy) and hyoscine *N*-butylbromide (60 mg) (Buscopan, Boehringer Ingelheim, Florence, Italy) was given intravenously to relax the smooth muscle of the biliary ducts.

A 7 Fr external biliary drainage catheter or internal–external catheter (straight flush angiography catheter or aortic pigtail; PBN Medicals, Stenloese, Denmark) was inserted into the biliary tree after cholangiography obtained either using the surgical T-tube or by percutaneous transhepatic access (Fig. 1A). After 3–5 days, various guidewires (Radifocus Guide Wire M, Terumo, Tokyo, Japan; Amplatz Super Stiff, Boston Scientific Medi-Tech, Watertown, MA, USA) and different types of 5 Fr catheters (Angled Taper or Cobra or Shepherd Hook, Terumo, Tokyo, Japan) were used and a balloon dilatation catheter (Courier; Boston Scientific Medi-Tech, Watertown, MA, USA) placed across the stenosis and inflated (10–30 sec in the same treatment) until the stenosis disappeared (Fig. 1B–D). Balloons 6–8 mm in diameter were used for dilatation of strictures extending into secondary bile ducts and a 10–18 mm balloon was used for the dilatation of the extrahepatic stricture. During these maneuvers mild intravenous sedation was given (diazepam, Biologici Italia Laboratories, Milan, Italy). An internal-external biliary drainage catheter (8–10 Fr) (Flexima, Boston Scientific Medi-Tech, Watertown, MA, USA) was inserted for a period ranging from 3 to 90 days (average 22 days) after bilioplasty. Cholangiography was performed to assess the result of the stricture dilatation. A second bilioplasty was performed in the case of stenosis recurrence.

Percutaneous treatment was concluded after patency assessment of the bile ducts and removal of the biliary drainage catheter.

Mechanical lithotripsy was performed using a 10 mm occlusion balloon catheter (Standard Occlusion Balloon Catheter, Boston Scientific Medi-Tech, Watertown, MA, USA) or saline flushing in 21 patients with lithiasis and/or sludge, in order to clear the biliary tree (Fig. 2A–C). Bilioplasty, with a 10 mm balloon catheter, was performed prior to attempting the passage of sludge and stones into the duodenum (Fig. 2B). Pharmacologic protection with octreotide, 0.1 mg three times a day (Longastatina, Italfarmaco, Milan, Italy), to avoid pancreatitis was given 3 days before and 3 days after the treatment in patients with an intact sphincter of Oddi.

Follow-up was done using clinical and laboratory assessment. All patients also underwent US and/or MR cholangiography to study biliary morphology after treatment.

When possible, a statistical chi-square test was employed. A $p$ value of less than 0.05 was considered significant.

## Results

All 51 patients underwent US Doppler examination to study hepatic artery patency. The Doppler scan was interpreted as abnormal in nine patients (4 patients with anastomotic stricture, 3 patients with anastomotic and intrahepatic strictures and 2 patients with intrahepatic stenosis).

No association was found between pre-OLT hepatic diseases and the presence of biliary strictures following OLT

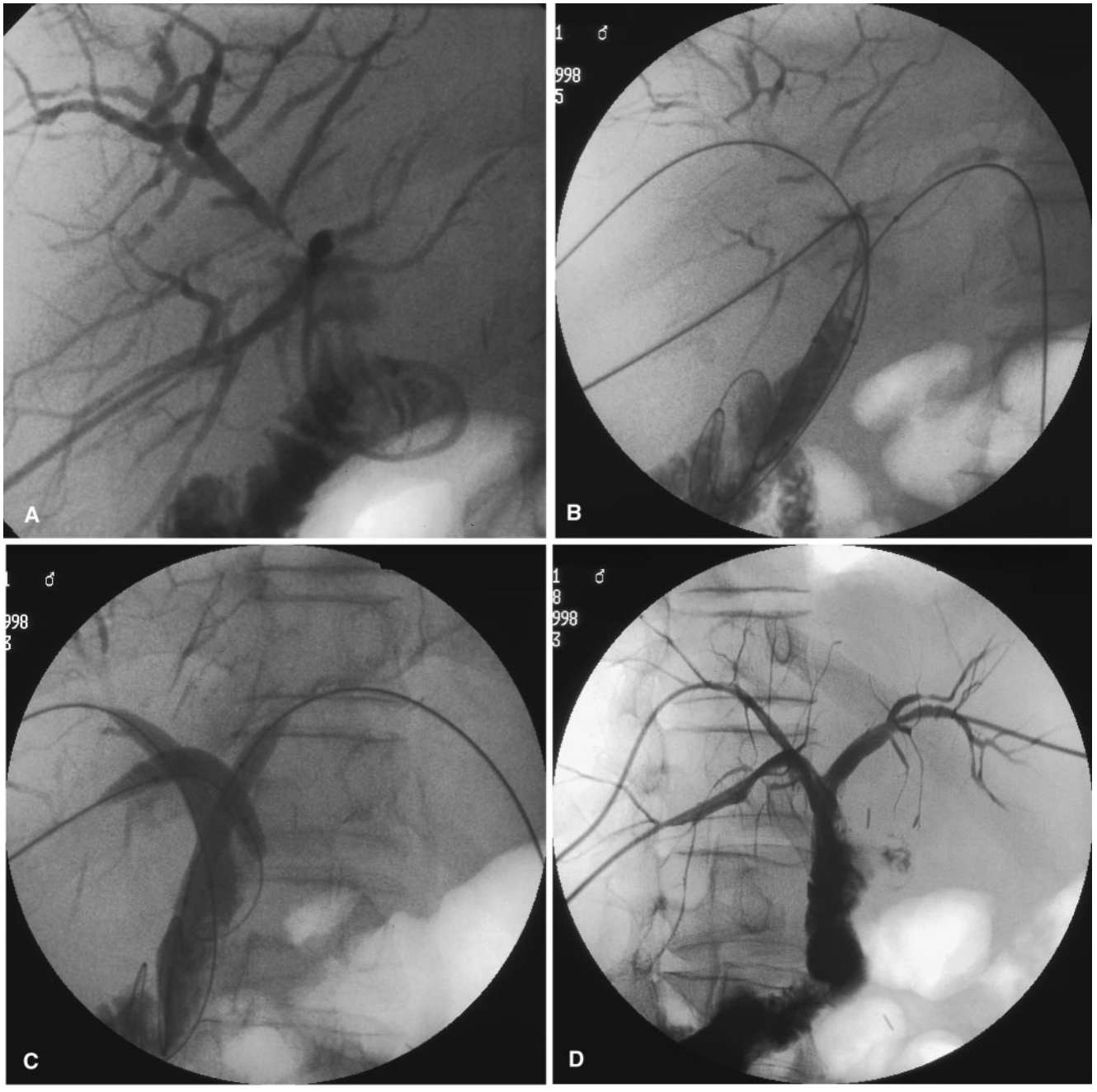


**Fig. 1. A–D.** A 57-year-old man with bilioenteric anastomosis after orthotopic liver transplantation (OLT). **A** Cholangiography obtained after transhepatic percutaneous insertion of an internal-external biliary catheter shows a biliary stricture which divides the fifth and eighth segment ducts from the sixth and seventh segment ducts. The left main bile duct is not opacified due to severe stenosis at the origin. **B, C** Three 10 mm diameter balloon catheters were positioned through the right and left bile ducts strictures (**B**) and inflated (**C**) simultaneously, performing a triple kissing balloon dilatation technique. **D** The cholangiogram after dilatation shows patent bile ducts, with excellent flow of contrast medium into the jejunal loop.

(Table 1). Neither was there found to be any association between the type of biliary anastomosis and biliary strictures complicating OLT ($p > 0.05$). We noted that six of 14 (43%) patients with CR-Y versus seven of 37 (19%) patients with CC anastomosis developed intrahepatic strictures ($p < 0.05$).

Two patients with split liver transplant were also treated.

## *Treatment Result*

Early technical success was obtained in all cases treated, avoiding the need for an immediate surgical repair.

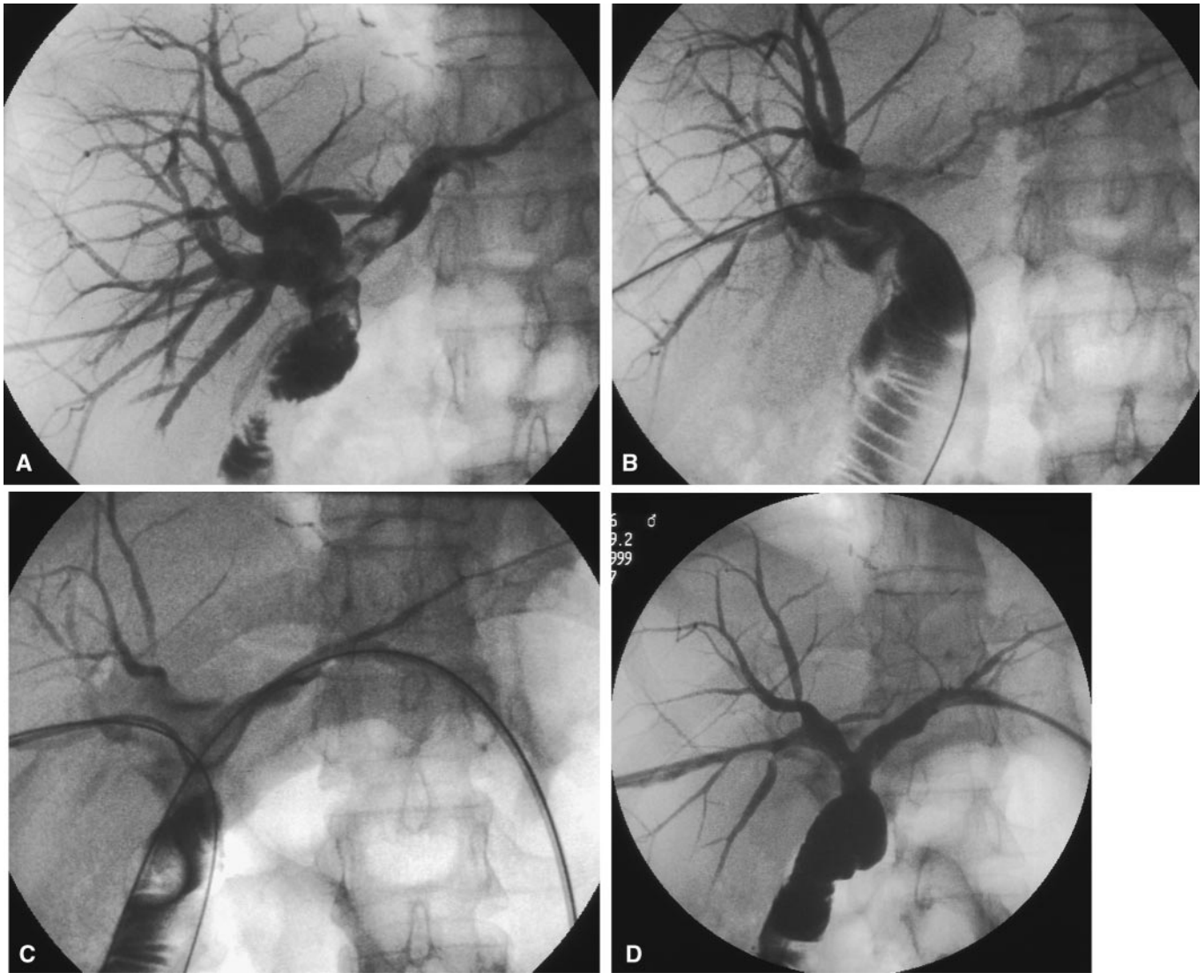


**Fig. 2.** **A–D**.A 43-year-old woman with CR-Y anastomosis after OLT. **A** Transhepatic percutaneous cholangiography shows an anastomotic stenosis, a 1.5 cm diameter stone in the common hepatic duct and several filling defects due to small stones and sludge in the intrahepatic ducts. **B** Dilatation with a 18 mm diameter balloon catheter is performed through the stenosis. **C** Mechanical litotripsy with an occlusion balloon catheter is performed using a left approach. **D** The final cholangiogram shows good flow of contrast medium into the jejunal loop and absences of stones.

Mild complications were observed after treatment in four of 51 (8%) cases: one acute pancreatitis which resolved spontaneously, two cases of hemobilia (spontaneously resolved after 3–7 days), one percutaneous fistula, successfully treated with acrylic particle embolization.

## *Survey Results*

A cohort of 33 of 51 (65%) patients were clinically followed for more than 12 months after percutaneous treatment, and included in the survey results.

Twenty-two patients required only one treatment, 11 of 33 (5 CC, 6 CR-Y) needed a second treatment at 1–41 months (mean 9.7 months) and of these latter three (3 CR-Y) required a third treatment at 4–23 months (mean 13.7 months).

US and MR cholangiographic imaging demonstrated patency of the bile ducts (13–58 months, mean 30.2 months) in 24 of 33 (72%) patients. Late stricture recurrence occurred 19 and 35 months after the last treatment in two other patients following three percutaneous treatments and a fourth bilioplasty was performed. For these two patients, further 12 month follow-up was not possible. Recurrent stenoses failed to be resolved by bilioplasty in six of 33 patients and surgical bilioenteric anastomosis was performed. A retransplantation in one patient was performed because of ischemic damage to the bile ducts.

The success of the treatment was seen to be independent from the type of anastomosis. The success rate was 14 of 20 (70%) in patients with CC anastomosis and 10 of 13 (77%) in those with CR-Y. Moreover, among the 11 patients needing multiple treatments, six (54%) had CR-Y anastomosis.

The presence of biliary stones had no negative influence on treatment success. In fact, 14 of the 33 patients simultaneously affected by bile duct stenosis and stones 12 (86%) were disease-free after one to three treatments. In only two of the 14 patients was a bilioenteric anastomosis performed.

## Discussion

Biliary tract complications are a recognized cause of substantial morbidity and mortality after hepatic transplantation [1, 3, 5, 8]. There have been many attempts by other authors to determine the etiopathogenic factors responsible for biliary complications [1–3, 6, 7, 9–17], to find an early diagnostic algorithm [1–8, 18] and describe the treatment of complications [2–6, 15, 18–25]. We have compared their conclusions with our experience.

### *Etiopathogenic Factors*

Hepatic artery occlusion is reported to be the most frequent cause of biliary strictures [9, 10]. Bile ducts are normally fed by the hepatic and gastroduodenal artery and their collateral vessels. During OLT collateral vessels are excluded from the hepatic artery anastomosis, which alone supplies the donor liver; in this condition a minimal decrease in hepatic artery flow may radically affect the biliary tree [11] inducing anastomotic and nonanastomotic ischemic bile duct strictures. Greif et al. [2] report that a hepatic artery thrombosis was found in 83% of patients with nonanastomotic bile duct strictures. Similarly, in our experience, patients with intrahepatic bile duct stenosis and nonanastomotic bile duct strictures showed decreased hepatic artery flow detected by US color Doppler (2/3 patients: 67%). This correlation seems less important in anastomotic strictures (9/38 patients: 15%).

In our experience, as in that of O'Connor et al. [12], no correlation was found between pre-OLT hepatic disease and biliary complications following OLT; this was confirmed by other authors [6, 7]. Risk factors for the development of biliary tract complications also include a small reduced-size liver transplant [1]. In our study we noted that two of 11 (18%) patients who received ex vivo split liver transplantation developed biliary strictures compared with 11% of patients with normal OLT. However, as the number of patients treated with split transplantation (11/619: 2%) is small these data are not statistically significant.

In agreement with Campbell et al. [6] we noted a higher incidence of intrahepatic biliary stenosis in patients with CR-Y than in patients with a C-C anastomosis. Also, as mentioned before there was a clear association between anastomosis type and stricture site.

As in the study by Greif et al. [2], our study demonstrated no correlation between the type of biliary anastomosis and biliary strictures complicating OLT ($p > 0.05$). Moreover, we found that patients with CR-Y required more interventional procedures than those with C-C anastomosis.

Other causes of biliary complications, including bile duct anatomic abnormalities [3, 7], prolonged cold graft ischemia time [12–14], ABO blood group incompatibility [6, 15] and cytomegalovirus infection [16, 17], have been reported by other authors but were not considered in this study.

### *Diagnostic Algorithm*

The diagnostic algorithm for patients with fever, hepatic allograft dysfunction, pain or clinical deterioration has a composite investigation based on clinical presentation (fever, ascites, jaundice, right upper quadrant pain), laboratory abnormalities (elevated levels of liver enzymes), and diagnostic imaging examinations (US, CT, MR cholangiography and T-tube cholangiography) [1, 8, 18].

In the case of suspected biliary complication the percutaneous approach usually follows to confirm the diagnosis and, at the same time, to carry out the appropriate therapeutic measures.

### *Treatment of Biliary Strictures*

According to other studies [2, 6] most biliary complications (80%) were treated within 12 months after OLT. Although no clear therapeutic algorithm has been reported to date, there are many approaches used to treat biliary stenoses, including surgical, endoscopic or percutaneous techniques.

Like Bouttier et al. [15] we believe that percutaneous treatment is the most appropriate choice in many cases as it is less traumatic than surgery and better accepted by this population of patients. However, in the presence of massive biliary leakage, portal vein thrombosis, chronic rejection, or severe and extensive biliary strictures, reoperation and retransplantation is needed [3].

We are not in complete agreement with Sheng et al. [18] who favor surgical treatment once lithiasis has been detected together with a biliary stricture: 46% of their patients with stones and/or sludge underwent surgical reconstruction. In our experience, 86% of patients with stenoses and stones or sludge can be successfully treated with the percutaneous approach.

Greif et al. [2] reported that in 94% of patients with bile stricture the C-C anastomosis was converted to a CR-Y. In 75% of patients with a primary CR-Y and biliary stricture, the anastomosis was surgically revised. In the literature 1-year biliary patency after surgical intervention ranges from 88% [15] to 89% [5].

In our study more than 70% of patients with biliary (C-C and CR-Y) stenosis were successfully percutaneously treated, exhibiting bile duct patency after 1 year.

The endoscopic technique was seen to successfully manage biliary strictures after OLT in 45–97% of patients [5, 21, 23]. In one report by Sherman et al. [21] there was a 4% procedure-related complication rate and a 2% mortality as a result of sphincterotomy.

The percutaneous approach is not complication-free: hemobilia, bleeding, cholangitis, pancreatitis, biliary fistula, bile duct perforation and duodenal perforation are well described in the literature, even if some studies [1–8] have reported no complications after percutaneous procedures. The complication rate was 8% in our series; the complications resolved spontaneously in 75% of cases. Moreover, the risk of bleeding, hemobilia, pancreatitis, and duodenal perforation are much higher with endoscopic procedures than with percutaneous techniques [5, 19, 21] and a CR-Y anastomosis does not allow for any endoscopic approach.

Therefore we chose not to use the endoscopic approach in patients with biliary complication after OLT in our institution; endoscopic treatment in skilled hands might be a reasonable alternative technique in other institutions.

The role of metallic stents for treating biliary strictures after OLT is unclear. Diamond et al. [24] and Culp et al. [25] treated a population composed of patients in whom initial balloon dilatation had failed. Metallic biliary stents are promising for intrahepatic strictures in transplanted patients, particularly those with widespread strictures [24]. Stents can be become partially or totally obstructed due to sludge and debris, but patency can often be restored with additional interventional techniques [24], even if long-term success depends heavily on repeat interventions or stent removal [25]. We believe that the use of metallic stents may complicate any subsequent surgical approach as they become embedded in the bile duct wall. If a percutaneous procedure fails then a surgical revision must still be possible [4, 19].

In conclusion, we believe that interventional radiology is an effective therapeutic alternative for the treatment of biliary complications after OLT with a high rate of success and should always be considered before surgical intervention. Elective surgery may be carried out in the few unresolved cases.

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