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Biliary complications after living donor adult liver transplantation*

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biliary anatomy assessment, biliary complications, liver transplantation, living donor liver transplantation, magnetic resonance cholangiography, split liver.

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Summary

The highest rate of complications characterizing the adult living donor liver transplantation (ALDLT) are due to biliary problems with a reported negative incidence of 22–64%. We performed 23 ALDLT grafting segments V–VIII without the middle hepatic vein from March 2001 to September 2005. Biliary anatomy was investigated using intraoperative cholangiography alone in the first five cases and magnetic resonance cholangiography in the remaining 18 cases. In 13 cases we found a single right biliary duct (56.5%) and in 10 we found multiple biliary ducts (43.7%). We performed single biliary anastomosis in 17 cases (73.91%) and double anastomosis in the remaining six (26%) cases. With a mean follow up of 644 days (8–1598 days), patient and graft survivals are 86.95% and 78.26%, respectively. The following biliary complications were observed: biliary leak from the cutting surface: three, anastomotic leak: two, late anastomotic strictures: five, early kinking of the choledochus: one. These 11 biliary complications (47.82%) occurred in eight patients (34.78%). Three of these patients developed two consecutive and different biliary complications. Biliary complications affected our series of ALDLT with a high percentage, but none of the grafts transplanted was lost because of biliary problems. Multiple biliary reconstructions are strongly related with a high risk of complication.

Introduction

In order to face the limited supply of organs available for transplantation, the adult living donor liver transplantation (ALDLT) is a valid option for patients considered appropriate, after a strict selection procedure, to receive a split liver. Indeed, a partial graft has a very high chance of success. The ALDLT procedure is relatively new and technically demanding. Medical and ethical aspects, related to the donor's safety and the recipient's care, are still a matter of debate. Accurate selection of both the donor and the recipient, and optimization of a few technical details should allow one to improve the rate of success of ALDLT [1–7].

According to many authors the highest rate of complications characterizing the ALDLT are because of biliary problems with a reported negative incidence between 22% and 64% [8–16].

This paper describes a retrospective analysis of a series of 23 consecutively ALDLT performed by our team. This paper focuses on the recipient's morbidity related to the overall biliary complications, and their management.

Patients and methods

From March 15, 2001 to September 30, 2005 we performed 23 right hemiliver transplants from living donors.

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The donors were 14 males and nine females with a median age of 37.8 years (25–64). Liver size and vascular anatomy were assessed by multislice computed tomography (MSCT) scan with vascular reconstruction. In the first five cases, we also used celiac and mesenteric angiography but then we concluded MSCT scan alone to be sufficient and reliable. We used celiac and mesenteric angiography only when anatomical findings by CT scan were not clear-cut.

Biliary anatomy was investigated using an intraoperative cholangiography alone in the first five cases. For the remaining 18 living donors, the biliary tree was studied with magnetic resonance imaging (MRI), with 1.5 T magnet and phased-array coil on the upper abdomen. For all these patients, magnetic resonance (MR) cholangiography was used, with T2 weighted imaging (fast spin-echo sequences), in coronal and axial acquisition. Ninety minutes after administration of a single dose of gadobenate dimeglumine (Gd BOPTA), a paramagnetic contrast agent with delayed biliary excretion, the analysis was completed with T1 weighted imaging that can visualize the contrast-enhanced biliary tree with thin (1.5 mm) gradient echo sequence in coronal plane (Fig. 1).

The paramagnetic contrast Gd BOPTA (Multihance®; Bracco, Milan, Italy) was injected at a standard dose of 0.1 mmol/kg, infused at rate of 2 ml/s. In the first nine cases of this study, in addition to MRI, we performed an intraoperative cholangiography on four patients. MRI was also used to determine the percentage of liver steatosis.

Right lobe transplantation was performed only when the graft-to-recipient weight ratio was above 0.8 (range 0.81–1.12). The volume of the donor's liver was measured by the CT scan.

The recipients were on the ordinary waiting list for cadaveric donor liver transplantation as United Network for Organ Sharing status 2B or 3. Recipient's median age was 51.86 years (27–63). The indications to the transplant were alcohol-induced cirrhosis ($n = 1$), hepatocellular carcinoma (HCC) in hepatitis B virus related cirrhosis ($n = 2$), HCC in hepatitis C virus related cirrhosis ($n = 12$), HCC in congenital hepatic fibrosis ($n = 1$), criptogenetic cirrhosis in Rendù Osler Syndrome ($n = 1$), hepatitis B virus related cirrhosis ($n = 1$), hepatitis B and C virus related cirrhosis ($n = 1$), hepatitis B and delta virus related cirrhosis ($n = 1$), primary biliary cirrhosis ($n = 1$), HCC in multiple adenomatosis ($n = 1$), and sclerosing cholangites ($n = 1$).

Blood groups for donor and recipient were identical in all of our cases. The transplant was carried out grafting the right donor hemiliver (segments 5, 6, 7 and 8) to the recipient. The resection line was defined by parenchymal demarcation obtained by clamping the right hilum and via intraoperative ultrasonography mapping the middle hepatic vein (MHV). The resection line was set a few millimetres from the right side of the MHV. In all cases the MHV was retained with the left hemiliver to ensure the best safety possible to the donor. The parenchymal transection was always performed using CUSA® Cavitron

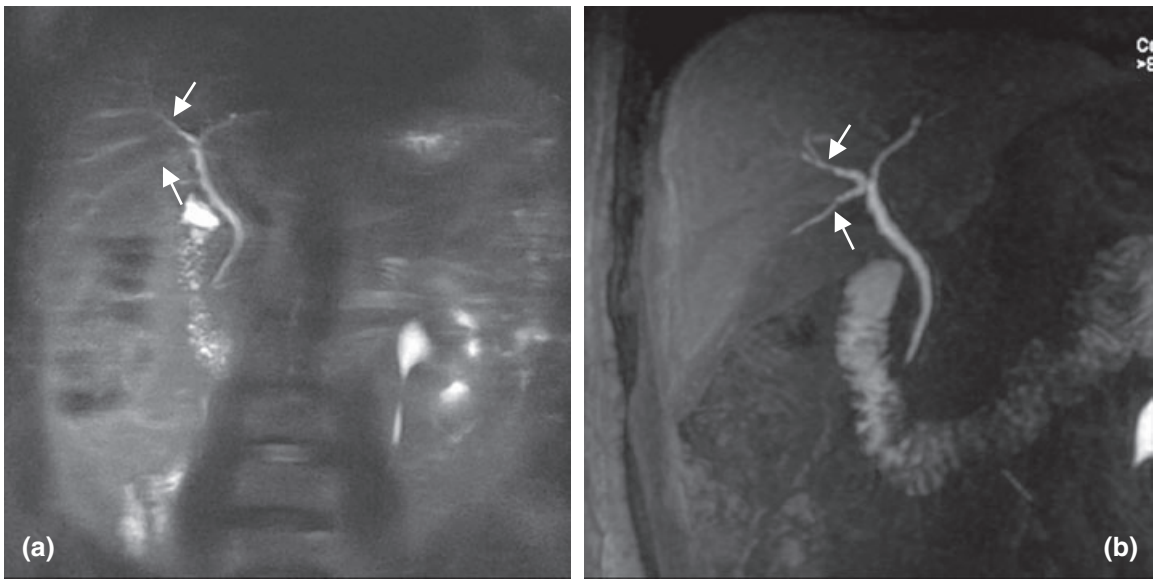

Figure 1 Two magnetic resonance imaging of the liver belonging to the same donor: (a) T2 weighted image taken without any contrast agent; (b) T1 weighted image taken 90 min after the administration of gadobenate dimeglumine. The white arrows show two main biliary ducts arising from the right hepatic lobe. The definition of the biliary tree in the cholangio magnetic resonance with the paramagnetic contrast agent is very accurate.

Ultrasonic Surgical Aspirator-Cooper Companies Inc. (Palo Alto, CA, USA), after dissection of the right biliary duct, of the right hepatic artery, of the right portal vein as well as of the right hepatic vein. All these elements were left attached to the right hemiliver. We used to cut the right biliary duct before the parenchymal transection and we controlled the bleeding from the cut surface of the biliary duct with suture ligation. We used low-power electro-cauterization when bleeding was minimal, and, even then, in very rare cases. The partial graft harvested from the donor was always perfused on back table with 1 l of Celsior® solution (Imtix-Sangstat, Lyon, France) in the right branch of portal vein and in the right hepatic artery. We always washed the biliary duct with the same solution. We have never used a venous–venous bypass surgery on the recipient and particular attention was given to achieve the best possible outflow [2–6, 17–25]. A couple of examples are described below.

We always performed a caval slitting or cavoplasty to assure the largest outflow in the anastomosis between the right hepatic vein and the vena cava. When the diameter of the accessory hepatic veins was larger than 5 mm, the veins were linked via anastomosis to the recipient vena cava. The portal and the arterial anastomosis were end-to-end between the right elements of the graft and the right or common vessels of the recipients. No interposition graft has ever been used. Table 1 summarizes the number of biliary ducts we found in every right graft and the kind of biliary anastomosis we performed in each transplant.

Whenever possible our first choice was to perform a direct anastomosis between the right hepatic duct of the graft and the common or the right hepatic duct of the recipient. When two ducts were present and in proximity to one another we performed a single anastomosis including both orifices possibly joined by a ductoplasty. When a direct biliary anastomosis was not possible because the ducts were more than two or were distant from each other, a Roux-en-Y hepatojejunostomy or an anastomosis with the cystic duct was performed [10,11,16,26–33]. In 13 cases, we found a single right biliary duct (56.5%) and in 10 we found multiple biliary ducts (43.47%) (seven double, three triple). In 17 cases (73.91%) we performed a single biliary anastomosis (16 duct-to-duct, one Roux-en-Y hepatojejunostomy) while in the remaining six cases (26%) we decided to perform a double anastomosis. If we take into consideration the multiple biliary reconstructions, on the recipient we used three times the right hepatic duct and the cystic duct, two times the right hepatic duct and a Roux-en-Y hepatojejunostomy, and one time the right and the left hepatic duct. All biliary anastomoses were performed with a running suture line using 5-0 polydioxanone (PDS®; Ethicon Inc., Somerville, NJ, USA). Eighteen times we drained the biliary system by a transanastomotic T tube and three times with a silastic catheter, first passed through the anastomosis and then exteriorized. These catheters are supposed to remain *in situ* for at least 3 months after the operation. Two times we did not drain the biliary anastomosis at all: in one case we practised a Roux-en-Y hepatojejunostomy, and in the second case the diameter of the biliary ducts was unusually large and we felt comfortable not to use a T tube across the biliary anastomosis [14,16,28,29,33,34].

The immune suppression was induced via the administration of rabbit-anti-thymocyte globulin, cyclosporine, azathioprine or mycophenolate mofetil and steroids. The immunosuppressive regimen was maintained with cyclosporine alone starting 1 month after the transplantation.

Table 1. Biliary anatomy and type of anastomosis.

No. ALDLT	No. of ducts	Type of anastomosis
Single biliary anastomosis 17/23 (73.9%)		
1, 2, 3, 8, 9, 12, 14, 16, 18, 19, 20, 21	1	Duct-to-duct
15	1	Roux-en-Y hepatojejunostomy
7, 11, 17	2	Ducto-plasty and duct-to-duct
23	3	Ducto-plasty and duct-to-duct
Multiple biliary anastomosis 6/23 (26.1%)		
6, 10	2	Duct-to-duct (RBD + RBD) AcD + CyD
5	2	RBD+Roux-en-Yhepatojejunostomy AcD(VII) + HD
13	2	RBD+RBD AcD+LBD
4	3	Ducto-plasty(RBD + AcD) and duct-to-duct AcD(VII) + Roux-en-Y
22	3	Ducto-plasty and duct-to-duct AcD(VI) + CyD

RBD, right biliary duct; LBD, left biliary duct; AcD, accessory duct; CyD, cystic duct; HD, hepatic duct; ALDLT, adult living donor liver transplantation.

Results

Rate of survival

With a follow up between 8 and 1598 days (median 644), 20 of the 23 transplanted patients are alive. Two of them have been retransplanted. These results show an overall patient's survival rate of 86.95% and an overall graft's survival rate of 78.26%.

Of the recipients three died, one died at postoperative (p.o.) day 7 because of massive pulmonary bleeding as a consequence of an arterio-venous fistula in Rendù-Osler syndrome [35]. A second one showed a weakly positive cross-match with the donor and received massive doses of immunosuppressive drugs. The recepient eventually died because of systemic aspergillosis on p.o. day 17. The third one with a primary graft disfunction developed systemic sepsis and biliary anastomotic leak. The recepient underwent relaparotomy to solve the leak before dying because of sepsis on p.o. day 39. Two recipients underwent retransplantation with a whole liver from a deceased donor. The first one showed arterial thrombosis at p.o. day 7 and the other one developed a small for-size syndrome with a consequent graft failure.

Biliary complications

The following biliary complications were observed: biliary leak from the cutting surface and consequent biloma: three times, anastomotic leak: two times, late anastomotic stricture: five times, early kinking of the choledochus: once.

These 11 biliary complications occurred in eight patients (34.78%). Three of these patients developed two consecutive and different biliary complications.

Three patients (13.04%) showed a biliary leak from the cutting surface and developed a biloma. They all were treated by placing a percutaneous drainage under CT scan control.

Anastomotic leak occurred in two patients (8.69%). The first one had a primary graft disfunction complicated by systemic sepsis and a small anastomotic leak. In p.o. day 9 the recipient underwent relaparotomy; a tiny leak was repaired by a direct suture and eventually died in p.o. day 39 with a poor functioning graft as a consequence of systemic aspergillosis. The second patient received a biliary duct to duct anastomosis during the transplant and developed a major anastomotic leak. The patient was reoperated and a Roux-en-Y hepatojejunostomy was performed.

Late anastomotic stricture occurred in five patients (21.73%) and developed between 2 and 6 months after the transplant. Of these patients, no one showed rejection episodes and consequently no one underwent any rejection treatment. Three of them had a previous biliary leak (two from the cutting surface, and one from the anastomosis) early after transplantation. All the anastomotic strictures were solved by endoscopic dilation and by placing a temporary trans-anastomotic stent. As far as cholangitis episodes are concerned, of the five patients who developed the biliary anastomotic stricture, three required hospital readmission because of biliary tree infections. Of these, two were readmitted before biliary stent placing and one after the endoscopic procedure.

Early kinking of the choledochus occurred in one patient, because of graft hypertrophy and was treated placing a temporary stent in the main biliary duct after developing a cholangitis episode. Biliary complications are given in Table 2.

The two patients without a tube across the biliary anastomosis did not show any kind of biliary complication.

Table 2. Biliary complications and treatment.

No. ALDLT	No. ducts	No. anastomosis	Type of anastomosis	No. complications	Management
4	3	2	Ducto-plasty (RBD + AcD) + HD AcD(VII) + Roux-en-Y	(1) Stricture	PTC/dilation/stent
10	2	2	Duct-to-duct (RBD + RBD) AcD + CyD	(1) Anastomotic leak	Relaparotomy(suture)
11	2	1	Ducto-plasty and duct-to-duct	(1) Stricture	PTC/dilation/stent
12	1	1	Duct-to-duct	(1) Leak/biloma	Percutaneous drenaige
13	2	2	Duct-to-duct (RBD + RBD) AcD + LBD	(1) Kinking	PTC/stent
19	1	1	Duct-to-duct	(2) Anastomotic leak + stricture	Relaparotomy(Roux-en-Y)
21	1	1	Duct-to-duct	(2) Leak/biloma + stricture	Percutaneous drenaige PTC/dilation/stent
22	3	2	Ducto-plasty and duct-to-duct AcD(VI) + CyD	(2) Leak/biloma + stricture	Percutaneous drenaige PTC/dilation/stent

RBD, right biliary duct; LBD, left biliary duct; AcD, accessory duct; CyD, cystic duct; HD, hepatic duct; PTC, percutaneous transhepatic cholangiography; ALDLT, adult living donor liver transplantation.

Discussion

The data from our experience confirm that biliary complications represent the major morbidity in the right lobe ALDLT [8–16,32,33,36]. The overall biliary complications were 11 (47.82%) and occurred in eight (34.78%) of 23 patients. A discussion on these results should first take into account the preoperative study of the donor in order to asses his/her biliary anatomy. As mentioned before, the living donors whose organs were used in operations 7–23 underwent MR cholangiography with Gd BOPTA as a biliary paramagnetic contrast. Gd BOPTA is a gadolinium-based agent of new generation; it is an intravascular-extra cellular and liver-specific agent. As a consequence of its properties, Gd BOPTA can be used both in MR angiography and in MR cholangiography to investigate the biliary anatomy in a delayed phase because 2–4% of its dose is excreted in the bile. Sometimes it is difficult to evaluate the biliary anatomy only by a T2 weighted imaging in the nondilated biliary tree and a supplementary T1 weighted imaging after administration of cholangio paramagnetic contrast, can add new anatomical findings complementary to the information obtained with T2 weighted sequence [37– 40].

Magnetic resonance is a noninvasive examination that allows one to study the biliary anatomy and the percentage of liver steatosis [41,42]. We found a very good correlation between anatomical biliary findings on the MR cholangiography and the clinical observations performed during the operation. On the operative field we never found unexpected patterns related to the biliary anatomy when the donor had been previously studied with an MR cholangiography. After case number 14, we suspended performing intraoperative cholangiography [4,43]. This allowed saving time during the harvesting operation and an easier organization in the operative room.

Three (13.04%) biliary leaks from the cutting surface occurred, with a consequent biloma. These leaks are probably a consequence of the cutting edge necrosis that impaired some ligatures or a consequence of unrecognized or missed small bile duct during surgery [36]. The back pressure on the biliary tree because of the edema of the papilla or of the hepatic duct anastomosis could be an alternative explanation for the occurrence of this complication. If this is the case, we think that the use of a trans-anastomotic T tube facilitating the bile flow could decrease the incidence of this kind of leaks [36].

In all these cases, we adopted a conservative procedure as suggested by our experience in split liver transplantation from cadaveric donors and in liver resection. We drained the biloma under CT scan guide and we left a drain *in situ* while waiting for the spontaneous resolution of the leak. Sometimes it took several weeks to solve but we think it is a procedure preferable to an aggressive approach with surgery. When reoperations were necessary because of the occurrence of this kind of problems, we observed a very fragile cutting surface altered by fibrin glue, when we used it, or by bile itself. It has been observed that very often it was not even possible to identify the leak and when found, occluding it with a suture was estimated to be very risky because of the 'rotten' cutting edge. In addition, sometimes the surgical manipulation could create a new damage to the surface with a consequent new bile leak or bleeding.

Two patients (8.69%) developed a biliary anastomotic leak. These kinds of complications are usually related to an ischemic injury of the anastomosis [14,16,36]. The right biliary system vascularization is at high risk of failure in this kind of split liver transplantation [14,44].The right biliary stump should be kept as short as possible and cut just inside the parenchyma. We think that the excessive dissection of the biliary stump facilitates the surgeon's task while performing the anastomosis but on the other hand places that same anastomosis at high risk of complication. Indeed, the recipient's biliary system devascularization can contribute to an early anastomotic leak, too. Nevertheless, we should not forget that ischemia of the biliary stumps is not always related to an excessive surgical dissection of the biliary tree. Some authors described an increased portal blood flow in a partial graft in the first days after transplant and a concomitant decrease of the arterial inflow [45–49]. These phenomena seem to be necessary steps for developing a small for-size syndrome, but the temporary decreased rate of the arterial flow could play a role in the biliary tree and biliary anastomosis ischemia.

The patients with biliary anastomotic leaks underwent a new laparotomy. In the first one we performed a new anastomosis using a Roux-en-Y hepatojejunostomy. The second patient was in very poor conditions, the anastomotic leak was very small and it was successfully solved by a direct suture. In our opinion the management of this kind of complications should take into account a surgical approach, particularly when the leak is remarkable. When facing this kind of complication, we incline to thinking that a new surgical intervention is the best way to proceed. Indeed, a direct view of the leak allows one to analyze the real damage and the vascularization of the biliary stump. And surgical repair is perhaps the best way to block this kind of leak [13,32,36,50–53].

Five patients (21.73%) showed a late anastomotic stricture. All were treated in a conservative way by multiple endoscopic dilation and by placing a trans-anastomotic biliary stent [13,50–53]. Of these five patients who developed strictures, two had a previous leak from the cutting surface and one had an anastomotic leak treated with a

new anastomosis using a Roux-en-Y hepatojejunostomy. Late biliary anastomotic strictures are usually related to chronic ischemia of the biliary stumps and we can expect an ischemic stump in patients who previously developed a significative anastomotic leak as discussed before.

We can now ask questions about the two patients who developed the late stricture after the cutting surface leak. Is there any correlation between the leak and the stricture? Our numbers are really too small to support this kind of correlation. We can just speculate that a biloma surrounding the biliary anastomosis could produce a local inflammatory reaction and create the initial condition for a late anastomotic stricture. We think that further experience will help to clarify this hypothetic correlation.

The last complication concerned one patient who developed an early anastomotic stricture because of an ipertrophic graft regeneration with consecutive biliary anastomotic kinking. The stricture was solved by placing a trans-anastomotic biliary stent. This kind of complication is very rare and we believe it is not possible to predict or to avoid it.

Our data confirm that biliary complications represent the major morbidity in ALDLT. Some questions are still open, relative to the best way to perform a biliary anastomosis. Yet, only direct anastomosis with the recipient biliary system or Roux-en-Y hepatojejunostomy are the two possibilities [16]. One could also ask whether the routine use of a trans-anastomotic T tube or a small catheter is still justified. Indeed, many authors report a significative reduction of morbidity after performing a duct-to-duct biliary anastomosis and after using devices to drain the bile flow outside. We started our experience in ALDLT always performing, when possible by anatomical point of view, a duct-to-duct biliary anastomosis and routinely placing a trans-anastomotic T tube. In our opinion a duct-to-duct biliary anastomosis is easier to perform, and it is more physiology-friendly when compared with a Roux-en-Y hepatojejunostomy. Moreover, it allows one to achieve an easy endoscopic retrograde cholangiopancreatography when needed [11,15,16,26,28,29,32]. Some authors report a high rate of complications related to the use of T tube such as cholangitis, leak nearby the insertion hole and leak after its removal. They suggest that the routine use of T tube be abandoned, as it is usually the case in whole liver transplantation [14,16,34]. Nevertheless, we point out that biliary anastomotic sections in partial grafts are smaller than the corresponding sections in whole liver transplants and that in the case of partial grafts an anastomotic edema with a consequent back pressure could facilitate a leak from the cutting surface. Another advantage offered by a T tube is the possibility to do a cholangiogram when a leak or an early stricture are suspected [14,16,32].

As far as the kind of sutures and the materials of suture are concerned, no consensus has been reached among authors [53]. We performed all the biliary anastomoses in our series using an absorbable monofilament in a running fashion. This seems to be related to a lower incidence of leaks but to a higher incidence of stricture when compared with the interrupted sutures. The Kyoto group performed the biliary anastomosis with continuous absorbable sutures [28] while the Hong Kong group preferred interrupted sutures with nonabsorbable monofilaments [29]. In the absence of published systematic randomized comparison of the two methods of suture, we relied on our own experience, which indicates that running suture never generated more complications than other methodologies. Nevertheless, we do agree that, when the ducts are very small, the interrupted fashion is more appropriate.

Our results could indicate that multiple biliary ducts in the right graft are related to an higher rate of complications if compared with graft with a single duct (40% multiple vs. 30.76% single). Yet, a closer scrutiny of the results reveal that what makes a significant difference in terms of increased morbidity is the presence of multiple biliary anastomoses. Among the six patients with multiple biliary anastomoses, four had biliary complications (66.66%), whereas among the 17 patients with single anastomosis, biliary complications occurred only in four (23.52%).

These findings might be expected (the more biliary ducts we find, the more complicated their reconstruction will be, and, the more anastomosis we performed, the higher the risk of a poor outcome) but some author did not find differences between the number of biliary anastomoses and their complication rate [14,16,54,55].

In conclusion biliary complications affected our series of ALDLT with a high percentage, but none of the graft transplanted was lost because of biliary problems. Most of the biliary complications were successfully treated without surgery by our interventional radiologists. Sometimes the patients who developed a biliary complication needed multiple treatment and consequent short hospital readmissions. The vast majority of the recipients had hepatocellular carcinoma matching the Milano criteria and a living donor was the only choice they had to be transplanted quickly.

We always recommend to perform a donor preoperative biliary anatomy assessment and, whenever possible, to avoid graft with multiple biliary ducts distant from each other to ease biliary reconstructions. This should also decrease the overall biliary morbidity along with a careful and limited dissection of the right biliary stump of the donor as well as of the bile ducts of the recipient in order to preserve their vascularization. We recommend

the use of a trans-anastomotic T tube to reduce the back pressure on the biliary tree and the use of suture ligation with fine needles to control bleeding from the cut surface of the bile duct. A sufficient liver mass indeed could avoid the possible biliary complications related to the small for size syndrome. Even doing so, biliary complications with their high rate of incidence still remain the Achille's heel of living donor liver transplantation and we finally believe that the key point of this kind of transplantation is giving to the recipient the proper liver mass that will allow the patient to overcome any biliary postoperative morbidity.

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