Hepatobiliary & Pancreatic Diseases International 18 (2019) 132–142

Contents lists available at ScienceDirect

Hepatobiliary & Pancreatic Diseases International

journal homepage: www.elsevier.com/locate/hbpd

Original Article/Transplantation

Adult-to-adult living-donor liver transplantation: The experience of the Université catholique de Louvain

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ARTICLE INFO

Article history:
Received 1 September 2018
Accepted 19 February 2019
Available online 28 February 2019

Keywords:
Liver transplantation
Living-donor
Hepatocellular cancer
Secondary liver tumor
Small-for-size syndrome
Small-for-size graft

ABSTRACT

Background: Liver transplantation is the treatment for end-stage liver diseases and well-selected malignancies. The allograft shortage may be alleviated with living donation. The initial UCLouvain experience of adult living-donor liver transplantation (LDLT) is presented.

Methods: A retrospective analysis of 64 adult-to-adult LDLTs performed at our institution between 1998 and 2016 was conducted. The median age of 29 (45.3%) females and 35 (54.7%) males was 50.2 years (interquartile range, IQR 32.9–57.5). Twenty-two (34.4%) recipients had no portal hypertension. Three (4.7%) patients had a benign and 33 (51.6%) a malignant tumor [19 (29.7%) hepatocellular cancer, 11 (17.2%) secondary cancer and one (1.6%) each hemangioendothelioma, hepatoblastoma and embryonal liver sarcoma]. Median donor and recipient follow-ups were 93 months (IQR 41–159) and 39 months (22–91), respectively.

Results: Right and left hemi-livers were implanted in 39 (60.9%) and 25 (39.1%) cases, respectively. Median weights of right- and left-liver were 810 g (IQR 730–940) and 454 g (IQR 394–534), respectively. Graft-to-recipient weight ratios (GRWRs) were 1.17% (right, IQR 0.98%-1.4%) and 0.77% (left, 0.59%-0.95%). One- and five-year patient survivals were 85% and 71% (right) vs. 84% and 58% (left), respectively. One- and five-year graft survivals were 74% and 61% (right) vs. 76% and 53% (left), respectively. The patient and graft survival of right and left grafts and of very small (<0.6%), small (0.6%–0.79%) and large (≥0.8%) GRWR were similar. Survival of very small grafts was 86% and 86% at 3- and 12-month. No donor died while five (7.8%) developed a Clavien–Dindo complication IIIa, IIIb or IV. Recipient morbidity consisted mainly of biliary and vascular complications; three (4.7%) recipients developed a small-for-size syndrome according to the Kyushu criteria.

Conclusions: Adult-to-adult LDLT is a demanding procedure that widens therapeutic possibilities of many hepatobiliary diseases. The donor procedure can be done safely with low morbidity. The recipient operation carries a major morbidity indicating an important learning curve. Shifting the risk from the donor to the recipient, by moving from the larger right-liver to the smaller left-liver grafts, should be further explored as this policy makes donor hepatectomy safer and may stimulate the development of transplant oncology.

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https://doi.org/10.1016/j.hbpd.2019.02.007

Introduction

Introduced in clinical practice in 1963 by Starzl, it took two decades before liver transplantation (LT) became recognized as a life-saving treatment for many acute and chronic end-stage liver diseases. Since then, surgical techniques, immunosuppressive therapies, perioperative and long-term medical care have been continuously improving. Nowadays, 1- and 5-year patient survival rates reach 90% and 70%, respectively. The discrepancy between numbers of available liver allografts and potential recipients is still responsible for 20%–30% waiting list mortality, in our center, during the last decade. Indeed, the initial favorable situation "more livers than recipients" rapidly inverted, despite continuous efforts to enlarge the liver allograft pool, and led to the development of surgical strategies, such as domino LT (limited due to the rarity of some well identified metabolic diseases), split LT (limited due to the reduced number of "good quality" organs) and cardiac-death donor LT (limited due to difficult logistic, legal and reduced organ quality). However, the only technical alternative that allows a substantial increase in LT is living-donor LT (LDLT). Unfortunately, the Western LT community, in contrast to the Eastern one, poorly embraces this approach (due to ethical and technical constraints), in spite of the increasing Western "popularity" of living-donor kidney transplantation.

The transplantation center of the Université catholique de Louvain (UCLouvain) embarked in 1994 on a pediatric LDLT programme. Four years later, the adult-to-adult LDLT (A2ALDLT) program was launched after several preparatory study visits to Japan and China. This paper presents a detailed analysis of the A2ALDLT UCLouvain experience. Lessons taken from this small single-center experience are discussed.

Methods

During the period of January 1998 to October 2016, 64 A2ALDLTs were performed at the Saint-Luc University hospitals in Brussels, Belgium. A detailed follow-up report is presented here. All events and results in both donors and recipients were classified following the European Liver Transplantation Registry criteria as early if occurring within three months and late if occurring later. Donor and recipient complications were classified according to the Clavien–Dindo classification [1]. Small-for-size syndrome was defined taking into consideration the Kyushu criteria (total bilirubin >20 mg/dL for seven consecutive days after post-LT day seven in absence of technical and immunologic factors [2–4] and the Hernandez-Alejandro's criteria (prolonged ascites, hyperbilirubinemia, INR or encephalopathy in absence of ischemia) [5]. The median follow-up of donor and recipient cohorts was 93 months (interquartile range, IQR 41–159) and 39 months (IQR 22–91), respectively.

Donor characteristics and procedure (Table 1)

One hundred twenty-two donor-recipient pairs were screened, in accordance to the requirements prescribed by the Institutional Review Board of the UCLouvain Faculty of medicine. The assessment included a mandatory evaluation by the deputy heads of the Departments of Internal Medicine and Psychiatry, both serving as "donor's advocates". Donor candidacy was rejected for medical reasons (obesity, diabetes and cardiovascular diseases) and/or insufficient graft-to-recipient weight ratio (GRWR) determined at ≤0.8% in patients presenting portal hypertension. Finally 64 selected donor-recipient pairs were selected. There were 34 (53.1%) female and 30 (46.9%) male donors; their median age was 34.8 years (IQR 27.6–46.2). The offspring composed the majority of donors (29 cases; 45.3%). ABO-incompatible LDLT was performed twice (3.1%). Thirty-seven (57.8%) LDLT was gender identical; 16 (25.0%) donor-recipient pairs were female-to-male and 11 (17.2%) male-to-female. Median donor body mass index (BMI) was 24.2 kg/m^2 (IQR 21.3–26.4). Pre-transplant liver biopsies were done in 19 (29.7%) patients in order to rule out steatosis. Eight specimens presented minor macro-steatotic changes and one a 30% macro-steatosis; living donation was performed after dietetic care.

During the first decade of our experience, anatomy and volumetry were determined using thin-slice angio-CT scan and cholangio-MRI; afterwards all 36 donors (56.3%) were worked-up using the MeVis software (MeVis GmbH, Bremen, DE).

All donor hepatectomies were performed or assisted by the leading surgeon (Lerut J), under combined general and epidural anesthesia. The incision consisted of a right subcostal incision extended to the right border of the right rectus muscle and to the xiphoid process. The decision to proceed with a right or left hepatectomy was based on the preservation of a minimal residual donor liver volume of ≥30% and to reach a GRWR of 0.8%. In the absence of recipient portal hypertension, the GRWR was deliberately lowered to 0.5%–0.6%. Very small and small-for-size graft were defined as those resulting in a GRWR of <0.6% and <0.8% (used in 7 patients each). For right-liver grafts, the hepatic venous allograft outflow was initially assured by including the middle hepatic vein in the graft and later on by draining ≥5 mm large segment V and/or VIII veins, using free vascular arterial or venous grafts from the post-mortem donor vessel bank.

In order to maximize donor safety and recovery, growing experience led to a progressive shift from the larger right (segments V to VIII) to the smaller left hemi-liver (segments I to IV) graft [6–8]. This shift was favored by the gradual increase of transplantation for primary and secondary liver malignancies.

The parenchymal transection was done combining bipolar water jet-coagulation and ultrasonic dissection combined with intermittent hilar clamping. Intraoperative cholangiography was performed three times: at the beginning of surgery (in order to detect eventual unknown anomalies), just before cutting the bile duct(s) (in order to optimize bile duct division) and after bile duct division (in order to verify integrity of the remaining biliary tree and to comply with possible medico-legal issues). The biliary transection plane was determined using a double metal wire identification method using two fine wires used in maxillofacial surgery sutured at the proposed transection plane. One infra-hepatic closed silicone drain was left in place for five days. Back-table work consisted of anterograde and retrograde rinsing of portal and hepatic veins as well as of the biliary tree using UW solution.

Because of security reasons, all donors stayed one day in the intensive care unit. Doppler ultrasound was done daily during the first five days in order to check the patency of the liver vasculature. Length of hospital stay was kept as short as possible in order to minimize infection risk. All donors had a MRI at six and twelve months in order to verify anatomy and regeneration of the residual liver. Donors were followed up yearly at outpatient clinic or contacted by telephone in order to document their physical and psychological evolution.

Recipient characteristics and procedure (Table 2)

Twenty-nine (45.3%) female and 35 (54.7%) male patients with a median age of 50.2 years (IQR 32.9–57.5) were transplanted. Thirty-six (56.3%) patients had a liver tumor: three (4.7%) had a benign tumor (alveolar echinococcosis, hemangiomatosis, and polyadenomatosis) and 33 (51.6%) a malignant tumor [19 (29.7%) hepatocellular cancer, 11 (17.2%) a secondary, bi-lobar and irresectable liver tumor (9 neuroendocrine and 2 colorectal metastases), and one each (1.6%) epithelioid hemangioendothelioma, hepatoblastoma and primary embryonal liver sarcoma]. Median

recipient BMI was 24.5 kg/m^2 (IQR 20.4–26.8). Median Child-Turcotte-Pugh and MELD scores were 7.5 (6.0–9.0) and 11 (IQR 7–16), respectively. Twenty-seven (42.2%) patients had a MELD score greater than 14; 22 (34.4%) recipients had no underlying primary parenchymal liver disease, and, consequently, no portal hypertension.

All transplant procedures included a vena cava sparing technique without use of veno-venous bypass. LDLT implantation was adapted to the optimal hepatic venous outflow and arterial inflow. In secondary liver tumors a coelio-mesenteric lymphadenectomy was performed. Venous outflow reconstruction was done by anastomosing donor and recipient hepatic veins in an end-to-end fashion. In left hemi-liver LDLT the hepatic veins of the graft are anastomosed to the widened cuff of the middle and left hepatic veins. In right hemi-liver LDLT a widening plasty was mostly added on the recipient inferior vena cava. Drainage of the anterior right allograft sector was restored depending on the volume of this sector and in case of GRWR <0.8%, by using free vascular grafts (see above). Hepatic artery reconstruction was done using magnifying loupes; in some cases the microscope was used. Graft inflow modulation, done either using splenic artery ligation (13/64, 20.3%) or embolization (2/64, 3.1%), was decided depending on the real allograft weight and the result of the intraoperative transit time electromagnetic flow measurement (>3 mL/g of liver tissue), done with adapted VeriQ flow probes (Medistim, Oslo, NO) [9]. Biliary reconstruction and drainage were adapted to diameter, number of bile ducts and judgment of the implantation surgeon.

All recipients had a similar postoperative infectious and tacrolimus-based minimization immunosuppressive treatment [10]. MRI and hepato-IDA scintigraphy were done at postoperative day 7 in order to document perfusion anomalies as well as function (excretion of the tracer) of the graft and (asymptomatic) biliary collections. Anti-thrombotic treatment consisted of low-molecular-weight heparin was used for the first postoperative month. Later on, patients received salicylic acid for six months.

Outpatient follow-up consisted of regular blood testing, Doppler ultrasound and systematic percutaneous or endoscopic control of the biliary tract, six months after LT and when clinically indicated. Cancer patients had three- to six-monthly thoraco-abdominal CT scan, bone scintigraphy and determination of tumor markers (CEA, DCP, CA19-9); in neuroendocrine patients six-monthly chromogranin A and DOTATOC PET/CT scan were added. In order to document biliary complications, endoscopic retrograde or percutaneous anterograde cholangiography were performed depending on the type of biliary reconstruction.

Statistical analysis

Continuous data were reported as median and IQR and tested with the Mann–Whitney *U* test, where appropriate. Binomial variables were reported as percentage and tested with Fisher's exact test, where appropriate. The time to events was analysed with the Kaplan-Meier method and compared with the log-rank test. The significance of statistical tests was taken at a P value <0.05. Analyses were run using SPSS (version 25.0; IBM Corp., Armonk, NY, USA).

Results

The donor procedure

The different features in relation to the donation of left- or right-liver grafts are displayed in Table 1. Over time, the team leant towards a more frequent use of left-liver grafts. During the first decade (1997–2006), 18 LDLTs were performed; 17 (94.4%) were right grafts and only one (5.6%) a left graft. During the second decade (2007–2016), 46 LDLTs were performed; 22 (47.8%) were right- and 24 (52.2%) left-livers. Accordingly, the follow-up after right hepatectomy was longer after right donation (116 months, IQR 64–189) than after left donation (53 months, IQR 31–95, $P < 0.001$).

The foremost difference between the left- and right-liver donation groups lies in the estimated remnant volumes. Right hepatectomy (including segments V to VIII) was performed in 39 (60.9%) and left hepatectomy (including segments I to IV) in 25 (39.1%) donors. In 17 (26.6%) donors, the middle hepatic vein was included in the right hemi-liver. Six (9.4%) and two (3.1%) grafts had a double arterial and portal supply and 15 (23.4%) and one (1.6%) grafts had two and three bile ducts, respectively.

The median predicted graft weight was 726 g (IQR 496–933) and the real median graft weight was similar (725 g, IQR 466–848, $P=0.469$). The median percentage of the remnant liver in the donor was 35% (IQR 31%–61%). The median estimated remnant-to-body-weight ratio was 0.69% (IQR 0.56%–1.15%).

Median operative time was 475 min (IQR 420–510). No donor required allotransfusion; 53 (82.8%) donors received intraoperative autotransfusion (median 300 mL, IQR 218–558) using the CellSaver® (Haemonetics, Braintree, USA). The median lengths of intensive care unit and hospital stays were 1 day (IQR 1–1) and 10 days (IQR 9–12).

Early donor morbidity following Clavien–Dindo was as follows: 16 (25.0%) patients had a grade I complication, 7 (10.9%) a grade II complication; one a grade IIIa (drainage for pleural effusion) and two (3.1%) a grade IIIb complication (reoperation for biliary leak from the cut surface and from an aberrant missed right duct. Two (3.1%) donors experienced significant temporary elevation of bilirubin level (IVa).

Accordingly, the total bilirubin peak was higher after right donation (2.6 mg/dL, IQR 1.7–4.2) than after left donation (1.6 mg/dL, IQR 1.2–2.0, $P=0.003$). Likewise, the INR peak amounted to 1.49 (IQR 1.32–1.64) after right hepatectomy, and to 1.27 (IQR 1.20–1.38) after left hepatectomy ($P<0.001$).

In one case, elevation of total bilirubin up to 21 mg/dL (in the absence of encephalopathy, ascites and coagulation disturbances) can be explained by a low estimated remnant volume (24%), even though preoperative MeVis imaging estimated the remnant-to-body-weight ratio at 0.40%.

Two (3.1%) patients needed repair of a midline incisional hernia 32 and 75 months after donation, respectively. During the entire follow-up, all donors remained in accordance with their initial decision to donate and none regretted donation. Only the patient who experienced severe liver dysfunction still has some psychological difficulties interfering with his daily life ("no drive anymore").

The recipient procedure

The different features of LDLT in relation to the type of graft are displayed in Table 2. The main difference between the two groups obviously is in graft weights and ratios. The predicted GRWR was 1.10% (IQR 0.81%–1.33%) while the real GRWR was 1.05% (IQR 0.82%–1.27%, $P=0.682$). The median graft weight, for left-liver recipients, was 454 g (IQR 394–534) and their median GRWR 0.77% (IQR 0.59%–0.95%), for right-liver recipients, the weight amounted to 810 g (IQR 730–940, $P<0.001$) and the GRWR to 1.17% (IQR 0.98%–1.40%, $P<0.001$). Thus, 21.9% (14/64) of recipients received a small-for-size graft. The actual GRWRs were less than 0.6% (very small graft) and between 0.6% and 0.79% (small graft) in 7 (10.9%) patients each and ≥0.8% (standard graft) in 50 (78.1%) recipients. Twenty-two (34.4%) patients did not present portal hypertension. Median operative time was 543 min (IQR 450–720). Cold ischemia time and warm ischemia time were 78 min (IQR 53–133)

Table 1
Data concerning living-donors.

Graft type	All grafts ($n=64$)	Left graft ($n=25$)	Right graft ($n=39$)	P value
Age (yr)	34.8 (27.6–46.2)	34.4 (27.0–50.4)	35.0 (27.9–42.8)	0.752
BMI (kg/m^2)	24.2 (21.3–26.4)	24.6 (22.9–26.9)	23.9 (21.2–26.0)	0.274
Donor-recipient relationship				
Related	48 (75.0%)	18 (72.0%)	30 (76.9%)	0.770
Child to parent	29 (45.3%)	11 (44.0%)	18 (46.2%)	1.000
Parent to child	6 (9.4%)	3 (12.0%)	3 (7.7%)	0.671
Sibling to sibling	10 (15.6%)	4 (16.0%)	6 (15.4%)	1.000
Other	3 (4.7%)	0	3 (7.7%)	0.275
Unrelated	16 (25.0%)	7 (28.0%)	9 (23.1%)	0.770
Spouse to spouse	4 (6.3%)	1 (4.0%)	3 (7.7%)	1.000
Friend to friend	3 (4.7%)	2 (8.0%)	1 (2.6%)	0.555
Families-in-law	8 (12.5%)	3 (12.0%)	5 (12.8%)	1.000
Other	1 (1.6%)	1 (4.0%)	0	0.391
Estimated remnant/liver volume proportion (%)	35 (31–61)	67 (58–71)	32 (30–35)	**<0.001**
Estimated remnant-to-body-weight ratio (%)	0.69 (0.56–1.15)	1.19 (1.07–1.36)	0.60 (0.51–0.69)	**<0.001**
Operative time (min)	475 (420–510)	475 (383–518)	470 (420–510)	0.725
Intraoperative blood loss (mL)[a]	300 (218–558)	300 (100–481)	330 (236–650)	0.255
Length of hospital stay (d)	10 (9–12)	10 (9–12)	10 (9–12)	0.873
Length of ICU stay (d)	1 (1–1)	1 (1–1)	1 (1–1)	0.311
Total bilirubin peak (mg/dL)[b]	2.0 (1.3–3.3)	1.6 (1.2–2.0)	2.6 (1.7–4.2)	**0.003**
ALT peak (IU/L)[b]	244 (199–334)	229 (199–367)	249 (198–328)	0.741
INR peak[b]	1.37 (1.23–1.54)	1.27 (1.20–1.38)	1.49 (1.32–1.64)	**<0.001**
Complications (Clavien–Dindo score)[c]				
I	16 (25.0%)	8 (32.0%)	8 (20.5%)	0.379
II	7 (10.9%)	2 (8.0%)	5 (12.8%)	0.696
IIIa	1 (1.6%)	0	1 (2.6%)	1.000
IIIb	2 (3.1%)	1 (4.0%)	1 (2.6%)	1.000
IVa	2 (3.1%)	0	2 (5.1%)	0.516
Follow-up (mon)	93 (41–159)	53 (31–95)	116 (64–189)	**<0.001**

ALT: alanine aminotransferase; BMI: body mass index; ICU: intensive care unit; INR: international normalised ratio.
[a] CellSaver® recovery.
[b] During the first postoperative month.
[c] Until discharge.

and 37 min (IQR 31–53), respectively. Forty-four (68.8%) patients needed transfusion (median 267 mL, IQR 0–1176).

Since the left graft is always procured with the middle hepatic vein, the necessity of venous outflow reconstruction prevailed in case of right-graft LT (64.1% vs. 24.0%, $P=0.002$). Venous outflow was reconstructed in 31 (48.4%) by means of vena cava plasty ($n=4$) or the use of a venous ($n=14$), or arterial ($n=12$) free vessel or a polytetrafluoroethylene graft ($n=1$). Graft inflow modulation was done in 15 (23.4%) recipients using splenic artery modulation because of excessive portal graft flow (>3 mL/g liver tissue) and small-for-size graft (7 cases). End-procedure hepatic arterial flow was 105 mL/min (IQR 59–148) for left grafts, and 150 mL/min (IQR 125–254, $P=0.003$) for right grafts. The difference in end-procedure portal vein flow [left: 505 mL/min (IQR 344–848) vs. right: 770 mL/min (IQR 600–1257), $P=0.012$] was annihilated when considering the weight of the graft (Table 2).

Biliary reconstruction consisted of duct-to-duct anastomosis (37 patients, 57.8%), Roux-Y hepatico-jejunostomy (26, 40.6%) and combined duct-to-duct and hepatico-jejunostomy (1, 1.6%). Biliary duct plasty was done in nine (14.1%) patients and three months long, internal biliary drainage was done in 44 patients (68.8%).

The median duration of intensive care unit and hospital stays were 3 days (IQR 2–10) and 20 days (IQR 16–31). Recipient morbidity recorded following the Clavien–Dindo classification was as follows: grade I in 7 (10.9%), grade II in 16 (25.0%), grade IIIa in 2 (3.1%), grade IIIb in 7 (10.9%), grade IVa in 8 (12.5%) and grade IVb in 15 (23.4%) patients. According to the Kyushu and Hernandez-Alejandro definitions of small-for-size syndrome, 3 (4.7%) and 15 (23.4%) recipients experienced liver insufficiency, respectively. Nine patients (14.1%) died (grade V) during the hospitalization of sepsis ($n=6$), perioperative cardiac arrest ($n=2$) and coeliac trunk dissection ($n=1$) following interventional radiology done the day before discharge to embolize a splenic artery aneurysm. Eleven recipients died later (>3 months) after LT of recurrent hepatocellular cancer ($n=4$), HCV ($n=2$) and alcoholic ($n=1$) allograft diseases, development of *de novo* tumor ($n=3$) and suicide ($n=1$).

Seven (10.9%) patients required early re-transplantation (re-LT) due to hepatic artery thrombosis ($n=2$), portal vein thrombosis ($n=2$) and one each due to coeliac trunk dissection, ruptured mycotic arterial pseudoaneurysm and graft dysfunction. Late re-LT was required six times due to intrahepatic biliary tract lesions ($n=4$), recurrent primary sclerosing cholangitis ($n=1$) and chronic rejection related to non-compliance ($n=1$).

Endoscopic or percutaneous biliary imaging was systematically done in all patients. Thirty (46.9%) recipients exhibited at least one biliary complication; 14 (21.9%) as early and 16 (25.0%) as late occurring events. Eight (61.5%) recipients, out of the 13 patients who presented multiple bile ducts and who survived the early postoperative period, developed biliary complications. Twelve (18.8%) patients experienced a biliary leak requiring surgical ($n=6$) and/or radiologic ($n=6$) and/or endoscopic ($n=3$) interventions. Twenty-two (34.4%) patients developed an anastomotic biliary stricture, requiring interventional endoscopy ($n=14$) and/or radiology ($n=16$); three times surgical correction became necessary. Ten (15.6%) recipients developed non-anastomotic biliary strictures; 5 patients (7.8%) finally required re-LT after several radiologic interventions.

Arterial complications were diagnosed in 10 (15.6%) patients. Two stenoses were balloon dilated. Early hepatic artery thrombosis was diagnosed in five patients; in three of them the quality of the artery was seriously compromised due to pre-LT long-standing steroid therapy, locoregional arterial chemo- and radio-embolisation. One recipient had a successful surgical redo, one interventional radiology, one medical treatment, while two patients actually needed re-LT. Two patients developed a hepatic artery pseudoaneurysm and underwent interventional radiology. One patient presenting a ruptured mycotic aneurysm in the

Table 2
Data concerning recipients.

Graft type	All grafts ($n=64$)	Left graft ($n=25$)	Right graft ($n=39$)	P value
Age (yr)	50.2 (32.9–57.5)	43.6 (26.7–52.9)	51.9 (35.3–60.4)	0.122
BMI (kg/m^2)	24.5 (20.4–26.8)	22.3 (18.8–25.7)	25.5 (22.4–27.7)	**0.005**
Indication for LT				
HCV-cirrhosis	9 (14.1%)	3 (12.0%)	6 (15.4%)	1.000
HBV-cirrhosis	3 (4.7%)	0	3 (7.7%)	0.275
Alcoholic cirrhosis	9 (14.1%)	4 (16.0%)	5 (12.8%)	0.728
Non-alcoholic steato-hepatitis	3 (4.7%)	0	3 (7.7%)	0.275
Cholestatic liver disease	12 (18.8%)	6 (24.0%)	6 (15.4%)	0.514
Autoimmune hepatitis	4 (6.3%)	2 (8.0%)	2 (5.1%)	0.640
Metabolic disease	4 (6.3%)	1 (4.0%)	3 (7.7%)	1.000
Budd–Chiari syndrome	2 (3.1%)	0	2 (5.1%)	0.516
Benign tumors	3 (4.7%)	0	3 (7.7%)	0.149
Primary tumors	22 (34.4%)	8 (32.0%)	14 (35.9%)	1.000
Hepatocellular cancer	19 (29.7%)	6 (24.0%)	13 (33.3%)	0.577
Primary undifferentiated embryonal liver sarcoma	1 (1.6%)	1 (4.0%)	0	0.391
Hepatoblastoma	1 (1.6%)	1 (4.0%)	0	0.391
Epithelioid haemangioendothelioma	1 (1.6%)	0	1 (2.6%)	1.000
Secondary liver malignancies	11 (17.2%)	7 (28.0%)	4 (10.3%)	0.092
Neuroendocrine tumor	9 (14.1%)	6 (24.0%)	3 (7.7%)	0.137
Colorectal carcinoma	2 (3.1%)	1 (4.0%)	1 (2.6%)	1.000
Child-Turcotte-Pugh	7.5 (6.0–9.0)	8.0 (6.5–10.5)	7.0 (6.0–9.0)	0.591
Class A	12 (18.8%)	3 (12.0%)	9 (23.1%)	0.338
Class B	20 (31.3%)	6 (24.0%)	14 (35.9%)	0.411
Class C	10 (15.6%)	4 (16.0%)	6 (15.4%)	1.000
Non-parenchymal liver disease	22 (34.4%)	12 (48.0%)	10 (25.6%)	0.105
MELD	11 (7–16)	10 (7–16)	12 (7–17)	0.431
MELD $\geq$14	27 (42.2%)	10 (40.0%)	17 (43.6%)	0.801
Estimated graft weight (g)	726 (496–933)	473 (399–526)	880 (750–993)	**<0.001**
Actual graft weight (g)	725 (466–848)	454 (394–534)	810 (730–940)	**<0.001**
Estimated GRWR (%)	1.10 (0.81–1.33)	0.73 (0.63–1.07)	1.18 (1.02–1.40)	**<0.001**
Actual GRWR (%)	1.05 (0.82-1.27)	0.77 (0.59-0.95)	1.17 (0.98-1.40)	**<0.001**
<0.6	7 (10.9%)	7 (28.0%)	0/39	**0.001**
0.6–0.79	7 (10.9%)	6 (24.0%)	1 (2.6%)	**0.012**
$\geq$0.8	50 (78.1%)	12 (48.0%)	38 (97.4%)	**<0.001**
ABO-incompatibility	2 (3.1%)	1 (4.0%)	1 (2.6%)	1.000
Middle hepatic vein in graft	27 (42.2%)	23 (92.0%)	4 (10.3%)	**<0.001**
Outflow venous reconstruction	31 (48.4%)	6 (24.0%)	25 (64.1%)	**0.002**
Graft inflow modulation	15 (23.4%)	9 (36.0%)	6 (15.4%)	0.074
Splenic artery ligation	13 (20.3%)	8 (32.0%)	5 (12.8%)	0.109
Splenic artery embolization	2 (3.1%)	1 (4.0%)	1 (2.6%)	1.000
Multiple hepatic arteries	6 (9.4%)	4 (16.0%)	2 (5.1%)	0.199
Multiple bile ducts	16 (25.0%)	1 (4.0%)	15 (38.5%)	1.000
Bile duct anastomosis				
Duct-to-duct	37 (57.8%)	13 (52.0%)	24 (61.5%)	0.605
Multiple ducts	5/37 (13.5%)	0	5/24 (20.8%)	0.147
Roux-Y hepaticojejunal	26 (40.6%)	12 (48.0%)	14 (35.9%)	0.436
Combined	1 (1.6%)	0	1 (2.6%)	1.000
T-tube	20 (31.3%)	7 (28.0%)	13 (33.3%)	0.784
Hepatic arterial flow before modulation (mL/min)	75 (36–167)	95 (30–95)	123 (55–123)	1.000
End-procedure hepatic arterial flow (mL/min)	119 (104–173)	105 (59–148)	150 (125–254)	**0.003**
End-procedure portal vein flow (mL/min)	540 (430–1072)	505 (344–848)	770 (600–1257)	**0.012**
Portal veinflow per 100 g graft weight (mL/min/100 g)	123 (80–166)	121 (83–174)	102 (72–158)	0.321
Cold ischemia time (min)	78 (53–133)	66 (49–126)	87 (54–133)	0.245
Warm ischemia time (min)	37 (31–53)	37 (31–57)	38 (31–53)	0.710
Intraoperative transfusions	44 (68.8%)	16 (64.0%)	28 (71.8%)	0.585
Intraoperative transfusion (mL)	267 (0–1176)	241 (0–721)	473 (0–1322)	0.330
Operative time (min)	543 (450–720)	555 (480–740)	510 (440–696)	0.432
Length of hospital stay (d)	20 (16–31)	20 (16–33)	18 (16–28)	0.411
Length of ICU stay (d)	3 (2–10)	4 (2–10)	3 (2–10)	0.248
SFSS (Kyushu)	3 (4.7%)	2 (8.0%)	1 (2.6%)	0.555
SFSS (Hernandez-Alejandro)	15 (23.4%)	7 (28.0%)	8 (20.5%)	0.553
Complications (Clavien–Dindo score)[a]				
I	7 (10.9%)	2 (8.0%)	5 (12.8%)	0.696
II	16 (25.0%)	4 (16.0%)	12 (30.8%)	0.243
IIIa	2 (3.1%)	2 (8.0%)	0	0.149
IIIb	7 (10.9%)	5 (20.0%)	2 (5.1%)	0.516
IVa	8 (12.5%)	3 (12.0%)	5 (12.8%)	1.000
IVb	15 (23.4%)	5 (20.0%)	10 (25.6%)	0.765
V	9 (14.1%)	4 (16.0%)	5 (12.8%)	0.728
Follow-up (mon)	39 (22–91)	31 (23–53)	71 (21–134)	0.085

BMI: body mass index; GRWR: graft-to-recipient weight ratio; ICU: intensive care unit; IQR: interquartile range; LT: liver transplantation, MELD: model for end-stage liver disease; SFSS: small-for-size syndrome.
[a] Until discharge.

context of a small biliary leak needed urgent arterial ligature followed by re-LT. Unfortunately, he died 15 months later due to the development of an aggressive Castleman disease.

Early portal vein thrombosis was diagnosed in 4 (6.3%) patients. One of them occurred in a patient who underwent graft inflow modulation and whose graft had two portal veins, so that the event was caused by a technical shortcoming. This patient died of pulmonary embolism just before further surgery. Two others were retransplanted and one patient underwent thrombolysis.

Hepatic vein stenosis was diagnosed in four (6.3%) patients: in three cases, as early complication and, in one instance, as a late complication. In three cases, widening of right hepatic vein was erroneously judged unnecessary due to the large diameter of the right hepatic vein. All three were treated by interventional radiologic stenting. The fourth one transplanted for Budd–Chiari syndrome with vena cava involvement, reconstructed with a peritoneal patch, developed allograft dysfunction in the context of a re-thrombosis of vena cava and hepatic veins; he died of sepsis after re-LT.

The 1- and 5-year actuarial patient and graft survival rates were 84% and 68%, and 75% and 60%, respectively (Fig. 1). Outcomes were comparable for right and left LDLT (Fig. 2) as well as for the different thresholds of GRWR (<0.6%, 0.6%–0.79%, and ≥0.8%) (Table 2 and Fig. 3). Survival of very small grafts was 86% and 86% at 3- and 12-month. Overall survival rates were similar to those obtained after deceased-donor LT done during the same time period (86% and 75% for 1- and 5-year patient survival, $P=0.534$); graft survival was somewhat better, although not significantly, in deceased-donor LT (83% and 70% for 1- and 5-year graft survival, $P=0.109$).

Discussion

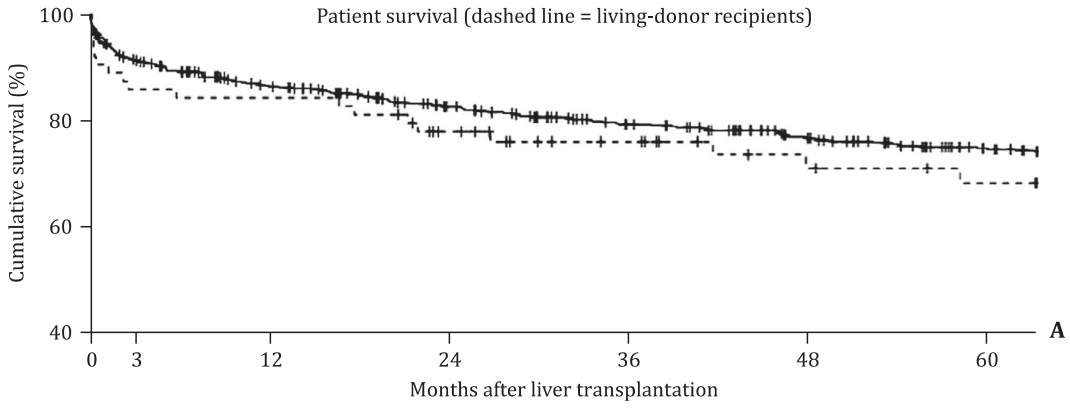
The first A2ALDLT using a left-liver (weighing 434 g) was performed by Makuuchi in 1993 at Shinshu University, Japan, in a female patient suffering from end-stage primary biliary cirrhosis [11]. This procedure was the start for a LT "tsunami" in the Eastern world. However, the enthusiasm for this procedure rapidly lost sympathy within the Western liver transplant community, as a result of a too high morbidity and even mortality in both donor and recipient surgeries. Today, very few Western centers perform A2ALDLT on a regular base [12,13]. Perhaps, many centers embarked on a LDLT program without sufficient knowledge of all the knacks and pitfalls of the complex, surgical and medical care of both donors and recipients. To avoid this, our center embarked on an A2ALDLT program following several tutorials and study visits in leading Asian centers. Our "real-world" experience shows that shortage of deceased-donor grafts and low-volume LDLT practice leads to a probably too rapid extension of indications, despite anatomical and clinical complexity in both donors and recipients.

The larger experience in hepatobiliary surgery without doubt explains the minimal risk of donor hepatectomy in Asian centers. Good outcomes are secured by precise preoperative knowledge of liver segmentation, of frequent vascular and biliary variations and of morphologic and functional graft (for the safety of recipients) and residual liver volumes (for the safety of donors) [3,14–17]. Every donor procedure should aim to procure the graft safely, leaving a sufficient residual liver volume in the donor. The residual liver volume should be more than 30% of the original volume; in older (>50 years) or steatotic donors this proportion should be raised to 35%–40% in order to cope with the reduced regeneration capacity [15]. Nowadays, quantification of steatosis can be calculated very precisely using mass-spectroscopy CT. If unavailable, a liver biopsy is advocated in donors with a BMI over 28 kg/m^2 [14,18,19]. In case of severe steatosis, dietary counselling, and physical exercise during 2 to 4 weeks help reduce the fat content and allow to proceed with donation [20]. Our experience confirmed that with good preoperative planning, donor hepatectomy can be done with minimal morbidity and no mortality.

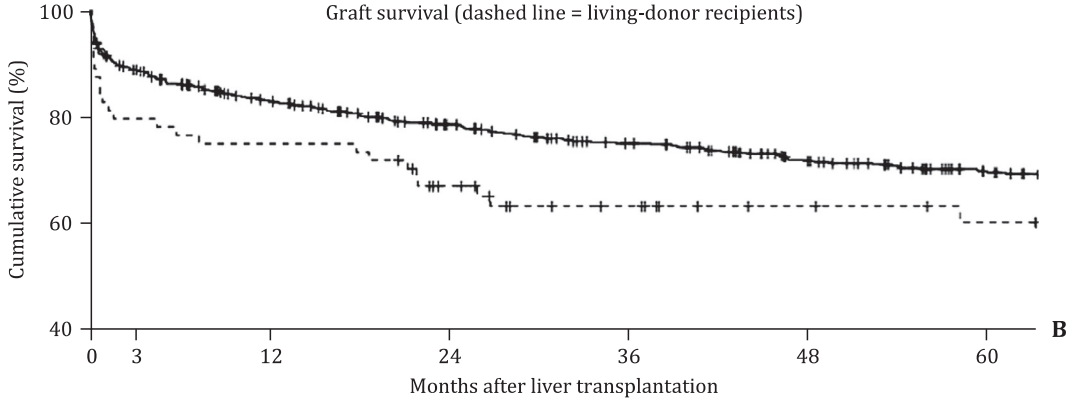
Besides disease severity and patient frailty, a successful A2ALDLT is highly dependent on the following four conditions: adequate graft volume, proper allograft outflow and inflow, and adequate biliary anastomosis [15]. The Kyoto group rapidly experienced that adequate liver volume is of utmost importance for a good outcome [21]. GRWR less than 0.8% [or correspondingly graft weight to standard liver volume (GW/SLV) less than 0.40] markedly reduced patient and graft survival, consequence of small-for-size syndrome. This condition is caused by intra-graft shear stress, a force associated with portal "overflow", which triggers arterial buffer response, in form of vasoconstriction, ultimately leading to arterial hypo-perfusion. These disturbances lead to the potentially unfavorable sequence of sinusoidal injury, excessive ineffective regeneration, severe cholestasis, impaired synthetic capacity and refractory ascites [2,22]. This chain of events is responsible for increased morbidity, prolonged hospital stay and higher costs, due to the intensive medical care including administration of large quantities of albumin and somatostatin [23].

In order to counteract small-for-size syndrome, several technical modifications of the allograft implantation, aiming to reduce portal vein flow and pressure, have been developed during the last two decades. The Kyoto group repeatedly reported that lowering portal vein pressure beneath 15 mmHg markedly improves outcome. If higher, graft inflow modulation, using proximal splenic artery obliteration and partial porto-systemic shunting, has been proposed. A more radical solution, consisting of interruption of venous collaterals along with splenectomy, has been advocated by the Kyushu group [24]. The excellent outcomes, obtained by these two approaches, have led the Kyoto and Kyushu groups to the more frequent (and successful) use of left-liver with GRWR as low as 0.6%. Their remarkable results triggered a shift from right (corresponding to a retrieval of 60% to 70% of liver mass) to left (corresponding to a retrieval of 30% to 40% of the liver mass) liver allografts. This policy allows not only to expand the donor availability but also to shift the risk from the donor (keeping a higher residual liver mass) to the recipient (receiving a lower liver mass) [3,6–8,24,25]. The implantation of a smaller liver graft mass in the presence of portal hypertension is riskier and reasonable only if both graft inflow and outflow are optimized, conditions that have to be assured based on intraoperative hemodynamic flow and pressure measurements. The modulation of portal and arterial inflow is the mainstay of graft flow control. The necessity for graft inflow modulation should be carefully evaluated, based on intraoperative flow and pressure measurements. Additionally, ligation of large portosystemic collaterals can improve portal vein flow [26]. Likewise, adequate venous outflow is of importance to avoid graft congestion, especially in right grafts. Optimization of hepatic outflow can be pursued by widening the anastomosis between hepatic veins and vena cava and/or by guaranteeing decongestion of the right anterior sector of the allograft by draining any segment V/VIII vein having a diameter larger than 5 mm. These veins can be connected to the vena cava or the cuff of middle and left hepatic veins using free venous or arterial grafts [15,27].

Biliary complications are the Achilles' heel of LDLT, with a reported incidence ranging from 10% to 67% [28–30]. The incidence of complications rises with the number of bile ducts to reconstruct. Likewise, our small series suffered from a high incidence of biliary complications. The high incidence of biliary complications reported in these series may be partly explained by the fact that our center developed a policy, based on an extensive experience in deceased-donor LT, to perform direct biliary imaging in every recipient, even in case of normal liver tests. Technical refinements are crucial elements to reduce the incidence of biliary complications. The three



Patient survival (%), $P = 0.534$					
DDLT	100	91	86		75
LDLT	100	86	84		68
Number of patients exposed to the risk of death					
DDLT	631	626	523		344
LDLT	64	64	54		26



Graft survival (%), $P = 0.109$					
DDLT	100	89	83		70
LDLT	100	80	75		60
Number of patients exposed to the risk of graft loss					
DDLT	631	626	501		324
LDLT	64	64	48		21

Fig. 1. Patient (**A**) and graft (**B**) survival rates after deceased-donor liver transplantation (DDLT) (full line) and living-donor liver transplantation (LDLT) (dashed line).

keys are minimal dissection during the donor procedure, in order to preserve the blood supply of bile ducts, microsurgical reconstruction and routine use of biliary drainage, during the recipient surgery [15,16,30,31]. The Seoul National University Hospital reported excellent results using the telescopic technique [32]. The use of biliary drainage remains a matter of debate. The worldwide most experienced center, Asan Medical Center in Seoul, strongly advocates routine *in situ* and internal-external biliary drainage for several months, in order to reduce biliary leakage. This approach also has the advantage to regularly control the biliary tree [15].

Our small experience confirms the impact of vascular complications on graft survival. Early arterial complications are reported in around 4% of adult LDLTs [33]. Results of arterial reconstruction can be improved using microsurgical techniques routinely, as shown by the Kaohsiung team [30]. Moreover, better handling of all different anatomic variations and modifications such as those caused by locoregional oncologic treatments (and unfortunately experienced in our series) is important to secure allograft arterialisation. Multiple surgical adaptations are "graft savers" in these situations and include extra-anatomical reconstructions using other arteries, instead of unusable hepatic arteries. Among these, we mention the recipients' right gastroepiploic (first choice), gastroduodenal, splenic, ileocolic and inferior mesenteric arteries, [31,32,34–43]. The incidences of portal and hepatic vein complications are similarly reported to be around 4%. In case of portal vein anomalies, several technical adaptations such as portal vein plasty and the Y-graft interposition have proven very successful [15,44–46].

In case of direct anastomosis, a wide plasty of hepatic vein and vena cava, eventually extended with a quilt venoplasty, is necessary to avoid (right) hepatic vein stenosis and thrombosis. Multiple hepatic veins are preferentially transformed to a common opening by using fresh or cryopreserved arterial or venous allografts or autologous saphenous vein [15,40,47]. These technical modifications will also counteract eventual stretching or compression of the anastomotic site by the regenerating liver [15,48].

The here mentioned, detailed, review of the complications encountered in the recipient as well as their management, involving

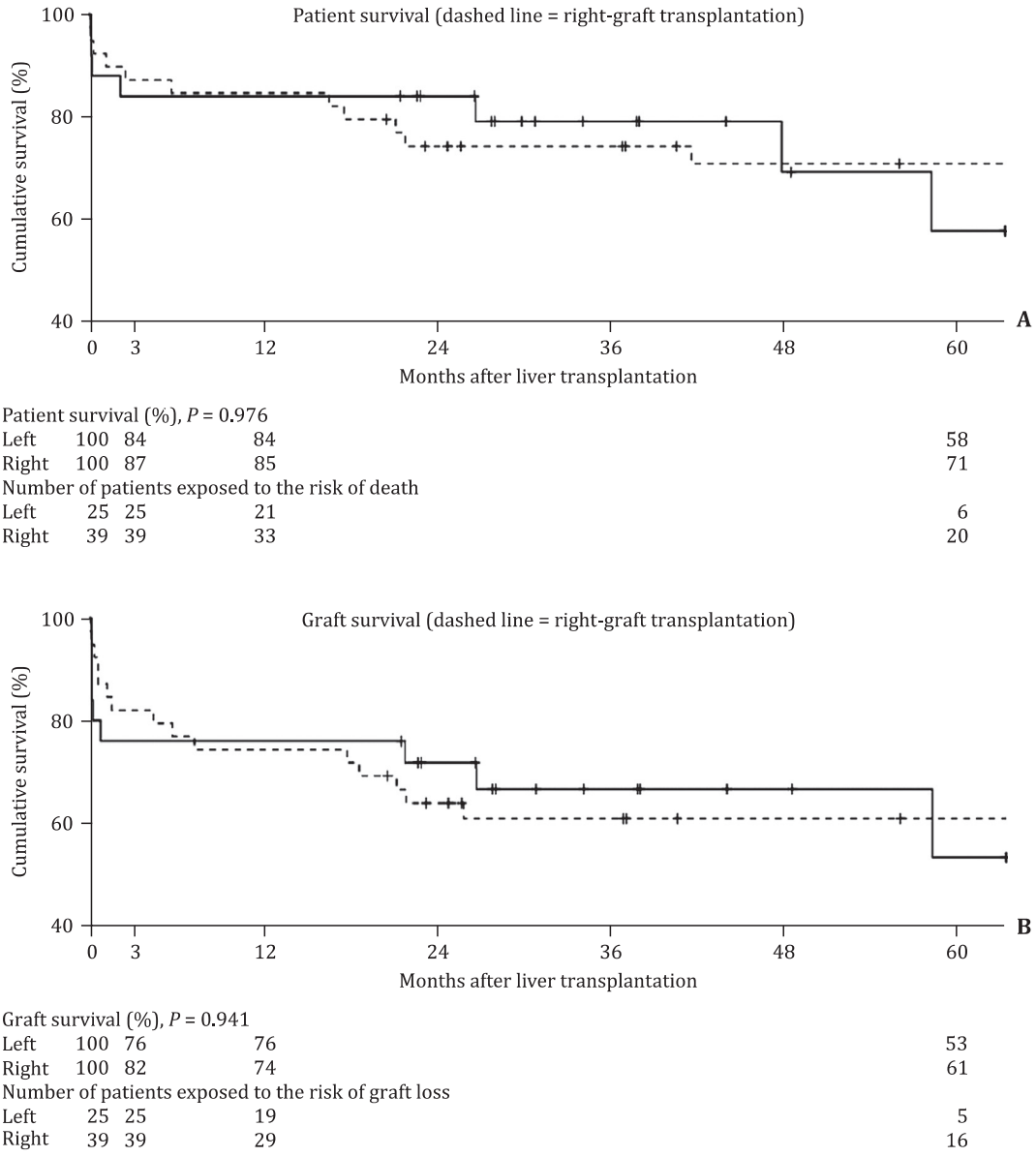
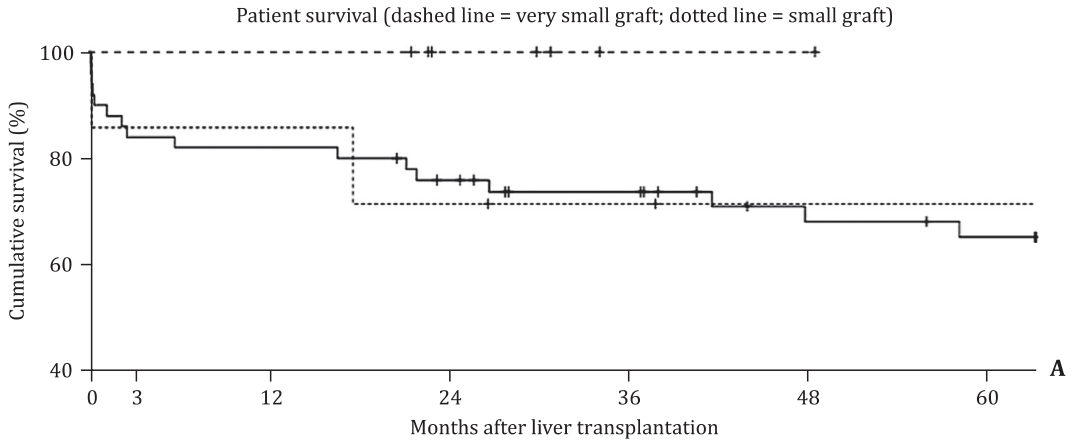


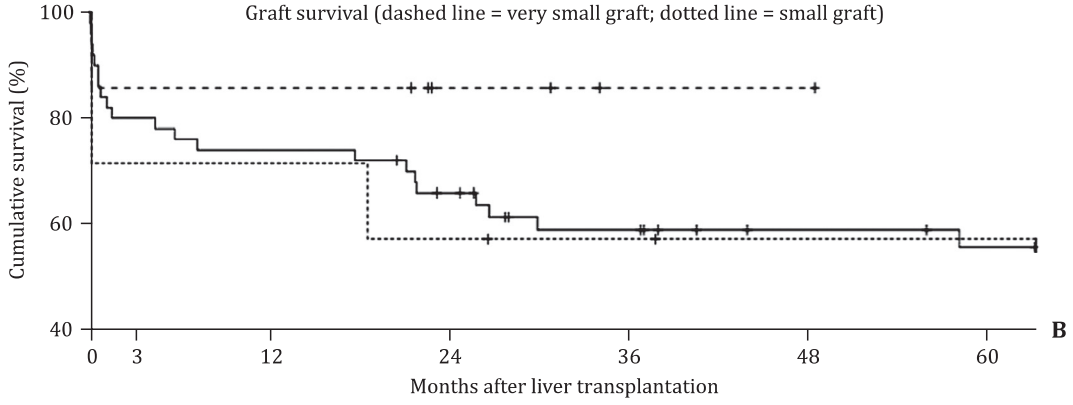
Fig. 2. Comparison of patient (**A**) and graft (**B**) survival rates after left-graft (continuous line) and right-graft (dashed line) living-donor liver transplantation.

surgeons, interventional radiologists and endoscopists, clearly indicate that the learning curve of A2ALDLT is long and complex. Open and repeated discussion of all encountered complications together with a perfect planning of both donor and recipient operations are the keys to progress and make the program successful: "there should be no surprises during the surgeries" [34].

At our center, LDLT is selectively offered to adults with low to no chance to be timely transplanted, as a consequence of the Eurotransplant organ allocation system. This applies in particular to patients suffering from autoimmune liver diseases [they have less chances to be transplanted because of their, usually, low body weight and preserved synthetic liver function resulting in low(er) MELD scores] and patients presenting advanced primary hepatobiliary and secondary liver cancers (not yet considered valid indications for LT). Therefore, LDLT represents for these patients (almost) the only chance to get access to a potential curative LT [49–52]. As such, our small experience underlines the value of A2ALDLT in the field of autoimmune diseases and transplant oncology. Indeed, 25% of patients were transplanted for autoimmune disorders and 56% for primary and secondary liver tumors. Liver metastases were the indication for LDLT in 17.2% of cases. In this setting, A2ALDLT has several advantages: (i) small left-liver grafts, with GRWR around 0.6%, can be used, in the absence of portal hypertension; (ii) interference with the scarce deceased-donor allograft pool is avoided for not yet validated indications for LT, avoiding ethical discussions about the justification of LT in such diseases; (iii) patients benefit from minimized and tailored immunosuppression; and (iv) basic oncological principles can be followed, implementing neo and adjuvant treatment protocols [53]. In the future, the choice of A2ALDLT is expected to be applied more frequently in the treatment of Milan-out hepatocellular cancer, cholangiocellular cancer as well as secondary liver tumors [50,54]. Additionally, LDLT will offer the opportunity to further explore, in a controlled way, the boundaries of inclusion criteria of cirrhotic patients harboring hepatobiliary tumors, as this approach controls both factors "tumor" and "time". The Eastern LDLT experience clearly showed that the Milan criteria are too restrictive [55–57]. Tumor morphology (number and diameter) and biology (tumor markers AFP, DCP or PIVKA-II and PET uptake), along with dynamic tumor behaviour (response to neoadjuvant



Patient survival (%), $P = 0.335$				
<0.6%	100	100	100	–
0.6% - 0.79%	100	86	86	71
≥0.8%	100	84	82	65
Number of patients exposed to the risk of death				
<0.6%	7	7	6	0
0.6% - 0.79%	7	7	7	3
≥0.8%	50	50	41	23



Graft survival (%), $P = 0.557$				
<0.6%	100	86	86	–
0.6% - 0.79%	100	71	71	57
≥0.8%	100	80	74	58
Number of patients exposed to the risk of graft loss				
<0.6%	7	7	6	0
0.6% - 0.79%	7	7	5	2
≥0.8%	50	50	37	19

Fig. 3. Patient (**A**) and graft (**B**) survival analysis per graft-to-recipient weight ratio (GRWR). Very small graft was defined as GRWR <0.6%, small graft was defined as GRWR between 0.6% and 0.79%.

locoregional therapies), are decisive for the fine-tuning of LT indication in hepatobiliary oncology. However, when LDLT is envisaged, the aggressive application of pre-transplant locoregional therapies (such as transarterial chemo- and radio-embolization) should be advocated with caution, because the arterial vessels risk severe damage so that the outcome of the transplant procedure can be compromised, a feature that was encountered in our series [43]. Recently, the Western transplant world has shown a renewed interest in LT for secondary liver tumors. Indeed, it has been shown that patients with non-resectable liver metastases from neuroendocrine and colorectal neoplasms can benefit from transplantation, when strict selection criteria are respected [58,59]. This indication is particularly important, in the context of LDLT, because these patients still have no access to deceased-donor LT and because the absence of portal hypertension permits the use of smaller left allografts safely.

In conclusion, A2ALDLT represents a major surgical and medical endeavor. Our small experience shows that living-donor hepatectomy can be done safely. The recipient operation still presents important morbidity, linked to biliary and vascular complications. Continuous technical refinements are necessary to reduce as much as possible recipient morbidity and mortality, in order to increase LDLT applicability, especially in the Western world. LDLT is a promising additive tool to the therapeutic armamentarium of the transplant surgeon and is worth a place, especially, in the treatment of primary hepatobiliary and secondary unresectable liver

tumors. The progressive shift, in our experience, from right- to left-liver grafting has to be considered in this context. The more frequent combination of the smaller (left) liver graft (up to 0.6% GRWR) use and both graft inflow and outflow modulation are required to optimize results and to make this procedure safe in both donor and recipient. By doing so, LDLT will avoid interference with the use of scarce deceased-donor allograft pool and will represent a boost to transplant oncology.

Acknowledgment

We thank Prof. Aude Vanbuggenhout for her kind linguistic revision.

Contributors

IS and LJ designed the study and drafted the article. IS, INME, RJJM, RC and LJ collected and analyzed the data. IS, CO, BRE, CL, GP and LJ critically revised the manuscript. All authors involved in medical care and approved the final version. LJ is the guarantor.

Funding

None.

Ethical approval

This study was approved by the Institutional Review Board of the UCLouvain Faculty of medicine.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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