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Living donor liver transplantation for hepatic malignancies in children

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Abstract

Background: Living donor liver transplantation is a treatment option for unresectable hepatic tumors in children.

Methods: We enrolled 45 living donor transplantations performed between 1993 and 2018 for liver malignacies, which included hepatoblastoma (n = 33), hepatocellular carcinoma (n = 10), hepatic angiosarcoma (n = 1), and rhabdomyosarcoma (n = 1).

Results: No mortality or major morbidities were encountered in any donor, and the complication rate was 9%. In the hepatoblastoma group, 5-year overall and event-free survival rate in recipients was 87.4% and 75.8%, respectively, and mortality was significantly higher in patients after rescue transplantation (p = .001). Inferior vena cava replacement in these recipients appeared to be associated with reduced mortality (p = .034), but this was not confirmed when rescue patients were excluded (p = .629). In hepatocellular carcinoma group, both 5-year overall and event-free survival rates were 75.4% each, and invasion of hepatic veins was significantly associated with increased risk of recurrence and death (p = .028). The patient with rhabdomyosarcoma died from EBV-induced lymphoma 2 months after transplantation. The patient with angiosarcoma was in complete remission at the last follow-up. Overall, 5-year graft survival rate was 81.3%, and one patient underwent re-transplantation due to chronic rejection.

Conclusions: Pediatric oncological liver transplantation has become a key player in the management of malignancies with cancer cure in 84% of patients in this series. Living donor liver transplantation for pediatric recipients with unresectable tumors might be a beneficial surgical option, which is technically safe for donors and recipients, thus, allowing timely planning according to chemotherapy protocols.

KEYWORDS
hepatoblastoma, living donor liver transplantation, malignancy

Abbreviations: AFP, alpha-fetoprotein serum level; CT, computed tomography; EBV, Epstein Barr virus; ECG, electrocardiogram; EFS, event free survival; F+, multifocality; HAS, hepatic angiosarcoma; HB, hepatoblastoma; HCC, hepatocellular carcinoma; HE, hemangioendothelioma; Ig, immunoglobulin; IVC, inferior vena cava; LD, living donor; LDLT, living donor liver transplantation; LM, liver malignancies; LT, liver transplantation; M+, metastatic disease; MRI, magnetic resonance imagery; NA, unknown; OS, overall survival; P+, portal vein involvement; PET, positron-emission tomography; POSTEXT, POSt-Treatment EXTent of disease; PRETEXT, pre-treatment extent of disease; PTLD, post-transplant Lymphoproliferative disease; R+, tumor rupture; R0, complete surgical resection; R1, microscopic incomplete surgical resection; RMS, Rhabdomyosarcoma; SIOPEL, International Childhood Liver Tumour Strategy Group; US, ultrasonography; V+, hepatic vein involvement.

1 | INTRODUCTION

Liver malignancies (LM) in children represent 1% of solid tumors with the commonest being hepatoblastoma (HB) followed by hepatocellular carcinoma (HCC).[1] In unresectable HB through partial hepatectomy, liver transplantation (LT) was later identified as a valid therapeutic option; in combination with cisplatin-based neoadjuvant/adjuvant chemotherapy, the long-term HB cure is more than 80%.[2–7] Due to chemoresistance in HCC, total tumor resection is the cornerstone of treatment.[8–10] In patients with underlying liver diseases (tyrosinemia, progressive familial intrahepatic cholestasis type 2, and other types of cirrhosis), regular liver screening and early detection of suspicious HCC nodules have been demonstrated to prompt surgical therapy with favorable prognoses, particularly, in the pediatric population.[11] In parallel with these advances in the management of LM in childhood, the implementation of living donor liver transplantation (LDLT) for pediatric recipients has been an additional surgical tool for unresectable LM for 30 years.[12] Particularly, in HB, which requires timely transplantation following recovery after the last course of neoadjuvant chemotherapy, LDLT allows for relief from the uncertain duration on the waiting list for a deceased liver donor.[13,14] Nevertheless, the apparent advantage of favorable timing of LDLT might be counterbalanced by the surgical risks in linving donors (LDs) and technical complexity in the recipients. Furthermore, when considering other pediatric LM, including HCC, the role of total hepatectomy with LT, particularly LDLT, remains unclear.

The aim of our study was to review the last 25 years of experience at our center in LDLT for pediatric LM in terms of the operative approaches proposed for radical resection as well as the technical, immunological, and oncological outcomes according to the histological type of LM. The present work also aimed to identify specific ethical issues relevant to the use of LD in advanced liver neoplasia in children.

2 | METHODS

The medical records of all patients aged <16 years who underwent LDLT for LM between July 1993 and December 2018 at the Cliniques universitaires Saint-Luc were retrospectively reviewed. This study was approved by the Institutional Review Board (No. 2020/19FEV/107). During this period, 441 LDLTs were performed; of them, 45 (10.2%) were for LM. The recipient data, including the demographic data, oncologic evaluations, surgical techniques, postoperative course, and tumor pathology were collected. In terms of the LDs, their demographic data, familial relationship with the recipient, surgical techniques, and outcomes according to the Dindo–Clavien scale were retrospectively collected.[15]

2.1 | Ethical protocol

The pediatric LDLT protocol at Cliniques universitaires Saint-Luc was approved by the Institutional Review Board in 1992 and subsequently revised in 2005, 2008, and 2016. This protocol describes the selection criteria as well as the medical work-up and psychological assessments of the recipients and LD who were strictly intrafamilial. Pre-assessment informed consent was obtained from all candidate LDs. If no contraindication was observed, a second informed consent form had to be signed preoperatively by the donor and his/her spouse as well as the recipient (according to his/her age) and his/her parents/guardians.

Oncological assessment and neoadjuvant therapy LM were categorized as HB, HCC, and other malignant tumors according to the histological analysis of the initial tumor biopsy and confirmed by that of the hepatectomy specimen. The initial diagnostic assessment included imaging to determine the tumor extension (Doppler [US], chest radiography, thoraco-abdominal [CT], abdominal [MRI], bone scintigraphy and/or [PET]-scan), alpha foetoprotein serum levels (AFP) , and tumor biopsy at diagnosis. In HB, PRe-Treatment EXTension (PRETEXT) determination was defined as previously published.[16,17] In HCC, the Milan criteria were assessed retrospectively based on both pre-transplant imaging and histological analysis of the specimens in cases of the multinodular cirrhotic liver.[9] Chemotherapy according to the successive International Childhood Liver Tumors.

SIOPEL protocols were administered preoperatively in all cases of HB.[6–8] The subsequent tumor response was evaluated using Doppler US and CT to assess the need for hepatectomy including "en-bloc" resection of the retrohepatic inferior vena cava (IVC) and/or portal vein. Vena cava replacement was systematically performed when the tumor was considered too close to IVC in PRETEXT and POST-treatment EXTension(POSTEXT) with an aim of R0 oncological resection.

LDs to rule out any increased operative risk, all donors underwent extensive medical assessment with biochemical analyses including thrombophilic assessment (protein C, protein S, antithrombin3, and activated protein C resistance), ECG, functional respiratory tests, and chest radiography. A specific consultation with an independent internist serving as the medical advocate of the LD candidate as well as psychological evaluation of the donor and his/her family were also organized. Liver imaging included hepatic Doppler US and MRI to determine the anatomy of the vascular and biliary tracts as well as to estimate the volume of the left lobe (SII-III) and left liver (SII-III-IV). Doppler US of the donor's internal jugular veins was also routinely performed to assess the caliber and permeability of both veins to allow the use of the left vein as a graft in the recipient's IVC replacement. Based on the weight of the child and MRI evaluation of the size of the left segments of the donor's liver, a left lobectomy (segments II and III) or left hepatectomy including the middle hepatic vein (segments II-III-IV) was performed in the donor with an aim of graft-to-recipient weight ratio >1%. Surgery was performed through a midline incision under general and epidural anesthesia.[18] The technical details of the left lobectomy and full left liver hepatectomy have been previously described.[19] If IVC replacement was indicated in the recipient, left internal jugular vein procurement

was also performed in the donor.[20] Postoperatively, the donors were monitored in the intensive care unit for the first 24 h. Daily routine biochemistry and Doppler US were performed until post-donation day six.

Surgical technique in recipients The surgical techniques in LDLT recipients have been previously described.[19,21,22] In the case of LDLT for LM, the first surgical steps in the recipient included the evaluation of hepatic and extra hepatic disease extension, confirmation of the impossibility of partial hepatectomy, and evaluation of the feasibility of total resection. To achieve complete resection, all adhesions were resected "en-bloc" with the hepatectomy specimen (including the scar and abdominal wall of any previous surgical biopsy). Ascites, if present, was analyzed using cytology. Total hepatectomy with or without vena cava resection was then performed under full clamping of the portal and IVC flow after performing a clamping test to confirm hemodynamic tolerance. Indication of vena cava resection was confirmed during the surgery if the tumor was found to be too close to the vein to ensure complete tumor resection. Biliary reconstruction consisted of an end-to-lateral Roux-en-Y hepatico-jejunostomy (length, 50 cm).

Post-transplant management All patients received current immunosuppression therapy protocols including tacrolimus and anti-CD25 monoclonal antibodies except for those who underwent transplantation before 2001 who had additionally received low-dose prophylactic steroids.[23] Acute cellular rejection proven by biopsy was treated with intravenous steroid boluses. In terms of post-LT oncological management, adjuvant chemotherapy was administered according to the chemotherapy protocol already administered preoperatively. The monitoring of serum AFP levels and regular imaging studies (liver ultrasound, thoraco-abdominal CT, and/or PET-CT) allowed the assessment of tumor recurrence, whose treatment consisted of chemotherapy and further surgical resection when possible.

2.2 | Statistical analysis

Survival was calculated using the Kaplan–Meier method with a minimum follow-up of 12 months and compared using log-rank tests for dichotomous variables and Cox regression for scalar variables. After normalization using Yeo and Johnson transformation, *p*-values were derived from the score test. All *p*-values are two-sided. Statistical significance was set at $p < .05$.

3 | RESULTS

Forty-five children underwent LDLT for primary LM ($n = 37$) or liver disease complicated by a malignant tumor ($n = 8$). The study population was categorized into an HB group (33 cases), HCC group (10 cases), and one case each of rhabdomyosarcoma (RMS) and hepatic angiosarcoma (HAS).

3.1 | HB group (Table 1)

3.1.1 | Pre-transplant assessment

The median age at diagnosis was 18 months (range: 4 days – 13.5 years; 15 males) Table 1. The initial median AFP was 315 000 ng/ml (range: 609–2 400 000). PRETEXT IV HB was observed at tumor diagnosis in 17/33 (51.5%) patients, whereas pre-treatment investigations demonstrated unresectable PRETEXT II and III in five and eight children, respectively. Three patients had "rescue" indications following a previous partial hepatectomy and secondary HB recurrence. Pulmonary metastases were detected at diagnosis in 10 (30.3%) patients. Biopsy of the liver tumor confirming the diagnosis of HB was performed in 28/33 patients (84.8%). All patients received preoperative chemotherapy (SIOPEL-2, 3, and 4 protocols). In the 10 patients with lung metastases, the metastases disappeared after preoperative chemotherapy in seven of them whereas the remaining three underwent thoracotomy metastasectomy (two bilateral; one unilateral) at a median interval of 47 days (range: 8–55) before LT. Among the three rescue cases, right hepatectomy (R0 margin) for PRETEXT II HB in one case and PREXTEXT III HB in two cases were previously performed. Two of them had received only adjuvant chemotherapy after partial hepatectomy, and HB recurrence in the left lobe was detected 6 and 57 months after the end of chemotherapy. The last patient's tumor demonstrated chemoresistance to neoadjuvant chemotherapy (SIOPEL-2 protocol, with the absence of tumor reduction before partial hepatectomy). In this patient, adjuvant chemotherapy was never interrupted before LDLT, and recurring disease was diagnosed in the left liver lobe 3 months after the primary surgery. A post-chemotherapy decrease in AFP was observed with a median pre-transplant AFP of 400 ng/ml (range: 24–41 447).

3.1.2 | Transplantation data

The median age at LT was 25 months (range, 3–171). Due to tumor proximity, the IVC has replaced in 27/33 (81.8%) cases. A portal vein jump graft was constructed in 2/33 (6.1%) patients due to portal cavernoma. During the hepatectomy phase of the transplantation, associated resection(s) was required to provide radical tumor resection with R0 margins as summarized in Table 1.

3.1.3 | Tumor pathology

Histology of the native hepatectomy specimen confirmed the diagnosis of HB. Details of tumor histology are presented in Table 1. Total resection with R0 margins was achieved in 32 (97%) cases whereas only one case had R1 margin at the level of a malignant thrombus inside the hepatic vein. All associated resections were malignancy-free. Tumor vascular involvement consisting of macroscopic and

TABLE 1 Demographics and transplant characteristics of 33 children with an HB treated with LDLT (*n* = 33)

Age at diagnosis	
Median (range)	18 months (0–162)
≥3 years	*n* = 11
≥8 years	*n* = 4
Gender	
Male/Female	15/18
Beckwith-Wiedmann Syndrome	*n* = 3
Tumor characteristics	
Pretext II	*n* = 5 (15.1%)
V+	*n* = 5
P+	*n* = 3
F+	*n* = 1
M+	*n* = 1
R+	*n* = 0
Pretext III	*n* = 8 (24.2%)
V+	*n* = 6
P+	*n* = 5
F+	*n* = 0
M+	*n* = 0
R+	*n* = 0
Pretext IV	*n* = 17 (51.5%)
F+	*n* = 9
M+	*n* = 9
R+	*n* = 3
Rescue	*n* = 3 (9.1%)
M+	*n* = 0
R+	*n* = 0
AFP at diagnosis	
Median (range)	315 000 ng/ml (609–2 400 000)
<100 ng/ml	*n* = 0
100–1000 ng/ml	*n* = 1
AFP pre-transplant	
Median (range)	400 ng/ml (20–41 447)
Age at LT	
Median (range)	25 months (3–169)
Caval replacement	*n* = 27 (81.8%)
Portal replacement	*n* = 2 (6.1%)
Associated resection	
Abdominal walls (biopsy scar)	*n* = 6
Omentum	*n* = 1
Diaphragmatic patch	*n* = 4
Adrenal gland	*n* = 1
Fascia of Gerota	*n* = 2
Partial splenectomy	*n* = 1
Histology	
Mixed epithelial/mesenchymal	*n* = 16
Epithelial fetal	*n* = 8
Epithelial fetal/embryonal	*n* = 6
HCC-like	*n* = 3
R0 margin	*n* = 32
R1 margin	*n* = 1
Vascular involvement	*n* = 14

Abbreviation: AFP, alfa-foetoprotein serum level; F+,multifocality; M+,metastatic disease; P+,portal vein involvement ; R+, tumor rupture; V+hepatic vein involvement.

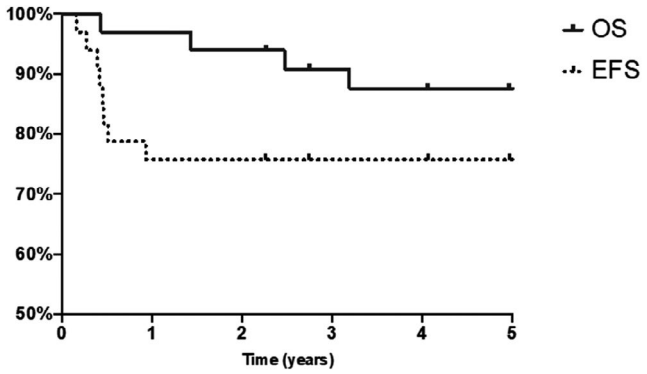

FIGURE 1 Overall survival (OS) and event-free survival (EFS) of HB group (*n* = 33)

microscopic thrombi and/or microscopic vascular permeation was identified in 13 (39.4%) cases.

3.1.4 | Oncological outcome and prognostic factors

Post-transplant chemotherapy was administered to 14/33 patients according to the SIOPEL protocol. After a median follow-up of 97 months (range, 5–241) after LDLT, 29 (87.9%) patients achieved complete remission (primary complete remission in 25 patients and secondary complete remission in four patients with HB). Among those with HB, eight patients developed tumor recurrence (24.2%) at a median interval of 5 months after LT (range, 2–11) (Table 3). Of these eight patients, two had pulmonary metastases at diagnosis that resolved after chemotherapy. Treatment of four metachronous pulmonary metastases included chemotherapy and resection with secondary complete remission after a median of 107 months (range, 67–173). The remaining four patients, including two who underwent transplantation for rescue indications, died of disease relapse at a median of 23 months after LDLT (range, 5–38).

The 5-year overall and event-free survival rates were 87.4% and 75.8%, respectively (Figure 1). The three patients who underwent rescue transplantation due to recurrence after partial hepatectomy demonstrated a significantly higher mortality rate than patients after

primary transplantation (66.7% vs. 6.7%, respectively, $p = .001$). The mortality rate was significantly lower when the recipient's retrohepatic IVC was resected en-bloc and replaced, than hepatectomy without IVC replacement (7.4% vs. 33.3%, respectively, $p = .034$). Nevertheless, after excluding patients with rescue transplantation, no differences in mortality rates were observed between patients in whom IVC was resected and those in whom it was not (7.7% vs. 0%, respectively, $p = .629$). Both overall and event-free survival rates were not affected by R+ at diagnosis, tumor focality, SIOPEL chemotherapy protocols (SIOPEL III vs. SIOPEL IV), quality of resection (R0 vs. R1 margins), or histological vascular involvement (data not shown).

3.2 | HCC group (Table 2)

3.2.1 | Pre-transplant assessment

Among the ten patients with multifocal HCC, eight had an underlying liver disease with cirrhosis, including five patients with type 1 tyrosinemia, one with portal agenesis in the context of Klippel–Trenaunay syndrome, one with mitochondrial disease, and one with type 2 progressive familial intrahepatic cholestasis Table 2. During the imaging follow-up of the eight patients with a cirrhotic underlying liver disease, suspicious nodules were identified in seven patients, and the remaining patient had micronodular liver. Among these eight patients with cirrhosis, two diagnoses of HCC were confirmed on five pre-transplant biopsies. Conversely, two patients had PRETEXT IV biopsy-proven HCC found in the clinical context of abdominal pain and hepatomegaly without any underlying liver disease. The initial median AFP level was 2989 ng/ml (range, 52–150 441). The two patients with HCC in the normal liver had very high serum AFP levels at diagnosis (139 650 and 111 332 ng/ml, respectively). Consequently, pre-transplant chemotherapy was decided according to the SIOPEL-3 high-risk protocol with a secondary decrease in serum AFP levels. No metastasis or lymph node invasion was detected on imaging assessments. Six patients were retrospectively found to meet the Milan criteria. Among the four patients transplanted outside from Milan criteria, one had a multifocal disease in cirrhotic liver with micro-nodules (maximum diameter ≤15 mm), and three had single macro-nodules (17, 13, and 12 cm, respectively) with satellite micro-nodules in two of them.

3.2.2 | Transplantation data

The median age at LT was 70 months (range, 22–168). The IVC was replaced in 4/10 patients. A portal vein jump graft was constructed in 2/10 patients due to portal cavernoma in one patient and portal agenesis in another. During the hepatectomy phase of the transplantation, associated resection(s) was required for radical tumor resection with R0 margins as summarized in Table 2.

TABLE 2 Demographics and transplant characteristics of 10 children with an HCC treated with LDLT ($n = 10$)

Gender	
Male/Female	8/2
Context	
Tyrosinemia	$n = 5$
PFIC2	$n = 1$
Mitochondrial disease	$n = 1$
Portal agenesis	$n = 1$
No underlying liver disease	$n = 2$
AFP at diagnosis	
Median (range)	2989 ng/ml (52–150 441)
<100 ng/ml	$n = 1$
100–1000 ng/ml	$n = 3$
Tumor characteristics	
Pretext II	$n = 4$
Pretext IV	$n = 4$
Rescue indication	$n = 1$
Not detected	$n = 1$
V+	$n = 3$
P+	$n = 2$
M+	$n = 0$
Age at LT	
Median (range)	70 months (22–168)
Caval replacement	$n = 4$ (40.0%)
Portal replacement	$n = 2$ (20.0%)
Associated resection	
Omentum	$n = 1$
Diaphragmatic patch	$n = 1$
Adrenal gland	$n = 1$
Histology	
Well differentiated	$n = 5$
Moderately differentiated	$n = 4$
Poorly differentiated	$n = 1$
R0 margin	$n = 9$
R1 margin	$n = 1$
Vascular involvement	$n = 7$ (70.0%)
Extrahepatic disease	$n = 1$ (10.0%)
Multifocal	$n = 10$ (100%)

Abbreviation: AFP, alfa-fetoprotein serum level; F+,multifocality; M+,metastatic disease; P+,portal vein involvement ; R+, tumor rupture; V+hepatic vein involvement.

3.2.3 | Tumor pathology

Histology of the native hepatectomy specimen revealed well-differentiated HCC in five cases, moderately differentiated HCC in four cases, and poorly differentiated HCC in one case. All eight patients with underlying liver diseases had cirrhosis on histopathology

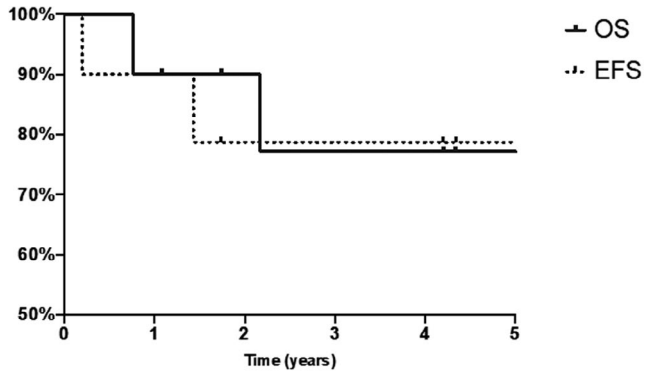

FIGURE 2 Overall survival (OS) and event-free survival (EFS) of HCC group (*n* = 10)

specimens. Total resection with R0 margins was achieved in 9/10 cases, whereas only one case included R1 margin at the level of extrahepatic microscopic nodules in the omentum. All lymph node specimens collected at the time of hepatectomy were free of malignancy. Tumor vascular involvement consisting of macroscopic and microscopic thrombi and/or microscopic vascular permeation was identified in seven cases.

3.2.4 | Oncological outcome and prognosis factors

After a median follow-up of 51 months (range, 12–218) after LDLT, 8/10 patients had achieved complete remission. Two patients (outside of Milan criteria) developed recurrence (20.0%), and both died of relapse 9 and 26 months after LDLT, respectively (Table 3). The first patient had no primary liver disease. Malignant portal vein thrombosis was observed on the initial hepatectomy specimen histology. Oncologic disease relapsed in the lung and liver 17 months after LT. The patient was subsequently treated with pulmonary metastasectomy and adjuvant chemotherapy but died 8 months after tumor progression. The second patient with tyrosinemia-related HCC had an omental nodule with vascular permeation on the pathology specimen at LT. The patient developed pulmonary metastases 2 months post-LT. Despite metastasectomy, the patient died of recurrence 6 months later. Both the 5-year overall and the 5-year event-free survival rates were 75.4% (Figure 2). Invasion of the hepatic veins on the native hepatectomy specimen appeared to be significantly associated with increased risk of recurrence and death (p = .028).

3.3 | RMS case

PRETEXT IV RMS with lung and mesenteric metastases was diagnosed in a 4.5-year-old girl. She received nine cycles of chemotherapy (ifosfamide, echinomycin-D, and vincristine) with a good response (disappearance of metastases). Exploratory laparotomy was then performed, including ascites cytology and omentectomy. Due to the presence of malignant cells in the omentum, abdominal and pulmonary radiotherapy was administered before LDLT. During LT, the IVC was replaced due to close contact with the tumor. Histology showed R1 margins with the presence of extrahepatic micro-nodules of RMS in the omentum. All lymph node specimens collected were free of malignancy, and no vascular involvement was identified. Chronic rejection proven by biopsy was observed precociously, 2 months after LT, and was treated with sirolimus. Concomitantly, she developed severe EBV-related stage III-IV lymphoma and died within a few days despite immunosuppression withdrawal and cyclophosphamide-based chemotherapy.

3.4 | HAS case

After the failure of right hepatic artery embolization, right hepatectomy was performed in a 3-year-old patient with a large 12 cm infantile HE. This surgery resulted in macroscopic invasion of the liver cut margin (R2) with the persistence of the hemangioma in the left lobe.

TABLE 3 Diagnostic and treatment features of tumor recurrence after LDLT for a liver malignancy (*n* = 10)

Patient's number	Age at diagnosis (months)	PRETEXT	Annotations	Initial AFP (ng/ml)	Histology	Vascular involvement
7	1	III	P+	83 000	HB Mixed	0
12	24	IV	V+,P+,F+	450 000	HB Mixed	0
15	11	II	V+	529 680	HB Mixed	0
23	18	IV	V+,P+,R+,M+	1231	HB Fetal epithelial	1
24	70	IV	V+,P+,M+	2 400 000	HB Fetal epithelial	0
29	12	II	V+,P+	1 957 941	HB Epithelial	0
30	49	Rescue	R+	89 000	HB Epithelial	0
31	166	Rescue		7260	HB Mixed	1
34	60	IV	V+,P+	139 650	HCC well-differentiated	1
36	102	II (cirrhosis on tyrosinemia)	V	150 441	HCC poorly-differentiated	1

Abbreviation: AFP, alfa-fetoprotein serum level; F+,multifocality; M+,metastatic disease; P+,portal vein involvement; R+, tumor rupture; V+hepatic vein involvement.

Four months later, the remaining lesions in the left lobe increased in size and number, and the patient complained of increasing asthenia. A new biopsy confirmed the diagnosis of benign hemangioma; LT was indicated due to the rapid tumor growth. The IVC was then replaced. Histology of the native hepatectomy specimen revealed HAS. The resection was complete (R0 margin), lymph node specimens collected were free of malignancy, and no vascular involvement was observed. The patient received four cycles of adjuvant chemotherapy (doxorubicin and ifosfamide) and was in complete remission at 126 months post-LT.

3.5 | Surgical complications **(Table 4)**

During the first 3 months after LDLT, 11 (24.4%) children experienced surgical complications (Table 4). IVC replacement was complicated by prosthesis thrombosis in 3/33 (9.1%) cases; all were treated with heparin therapy with subsequent resolution. One additional patient needed a surgical redo on day 1 after LT for Budd–Chiari syndrome (significant clinical ascites and reverse portal vein flow with no hepatic vein flow on US), and a recipient jugular vein was interposed secondarily between the thrombotic left hepatic vein and IVC prosthesis. No hepatic artery thrombosis was observed in this series. In the long-term, 7/45 (15.5%) patients developed biliary stenosis; of them, six were treated by surgery (anastomotic stricture) and one by percutaneous dilatation (anastomotic and intrahepatic strictures) at a median interval of 15 months after LT (range, 3–29). Portal vein replacement in a patient with HCC and portal agenesis was complicated by thrombosis extending to the Rex recessus and treated with a meso-caval shunt at 46 months post-LT. The occurrence of surgical complications did not significantly influence the risk of tumor recurrence or death. There was no statistical difference in terms of complications (acute, chronic, and rejection) between the HB and HCC groups.

Biopsy-proven acute cellular rejection was observed in 17/45 (37.8%) children; 12/33 (36.4%) with HB, 4/10 (40%) with HCC, and one with RMS. Chronic rejection was observed in two patients, one transplanted for HB and another for RMS, and were treated with sirolimus. One of them, in HB group, required liver re-transplantation combined with kidney transplantation for chronic kidney insufficiency related to previous chemotherapy (cisplatin, doxorubicin, and carboplatin) 22 months after the first LDLT with uneventful long-term follow-up. In total, 24 EBV-negative recipients received a graft from an EBV-positive donor (54.5%). Of them, only one patient who underwent transplantation for RMS developed severe EBV-related stage III-IV lymphoma and died 2 months post-LT despite immunosuppression withdrawal and cyclophosphamide-based chemotherapy.

3.6 | LDs (Table 5)

All donors were intrafamilial with a majority being parents (37/45, 82.2%), and the median age at donation was 35 years (range, 24–52) Table 5. The left internal jugular vein was procured from 33/45 (73.3%) LDs for recipient IVC replacement. No postoperative donor mortality was encountered in this series with a minimum follow-up of 1-year post-donation. The median hospital stay was 8 days (range, 6–10). Forty-one (41/45, 91.1%) donors had no postoperative complications, whereas two required antibiotics for cholecystitis and urinary tract infection, respectively (Dindo–Clavien score II). One donor required antibiotics for urinary tract infection and temporary percutaneous drainage of a collection at the liver cut surface under local anesthesia (Dindo–Clavien score IIIa). Another donor underwent surgery for incisional hernia 21 months after donation under general anesthesia (Dindo–Clavien score IIIb).

4 | DISCUSSION

The role of LT for unresectable HB has progressively emerged and is well established.[7] In the most recent decade, thanks to the evolution

Margin	Interval LT/recurrence (months)	Recurrence	Treatments	Outcome	Follow-up (months)
R0	5	Lung	Chemotherapy/surgery	Complete remission	173
R0	5	Lung	Chemotherapy/surgery	Complete remission	113
R0	4	Lung	Chemotherapy/surgery	Complete remission	101
R0	3	Lung	Chemotherapy/surgery	Complete remission	67
R0	6	Lung, brain	Chemotherapy/surgery/radiotherapy	Died	38
R0	2	Lung	Chemotherapy	Died	5
R0	11	Local	Chemotherapy	Died	17
R0	5	Lung,brain,bones	Chemotherapy	Died	29
R0	17	Local, lung	Chemotherapy/surgery	Died	26
R1	2	Lung	Surgery	Died	9

TABLE 4 Overall post-transplant complications in 45 children after LDLT for a liver malignancy

	HB group (*n* = 33)	HCC group (*n* = 10)	RMS (*n* = 1)	HAS (*n* = 1)	Total (*n* = 45)
Surgical complications <3 months	*Treatment*	*Treatment*	*Treatment*	*Treatment*	
IVC thrombosis	2 Heparin	1 Heparin	0	0	3 (6.7%)
Hepatic vein thrombosis	1 Surgery	0	0	0	1 (2.2%)
Femoral vein thrombosis	1 Heparin	0	0	0	1 (2.2%)
Occlusive syndrome	2 Surgery	1 Surgery	0	0	3 (6.7%)
Biliary leaks	3 Surgery	0	0	0	3 (6.7%)
Haemorrhage/ hematoma	3 Surgery	0	0	0	3 (6.7%)
Surgical complications >3 months					
Biliary stricture	5 Surgery	1 Percutaneous dilatation		1Surgery	7 (15.9%)
Occlusive syndrome	0	1 Surgery		0	1 (2.3%)
Portal vein thrombosis	0	1 Surgery		0	1 (2.3%)
Pre-transplant EBV status					
Recipient IgG +	9	5	0	0	14 (31.1%)
Donors IgG+	30	7	1	NA	38 (86.4%)
Donors IgG+/ Recipient IgG-	22	1	1	NA	24 (54.5%)
Rejection					
Acute	12	4	0	1	17 (37.8%)
Chronic	1	0	0	1	2 (4.4%)

TABLE 5 Demographics, surgical data, and postoperative complications in 45 LDs of liver grafts for 45 children with liver malignancy

	HB group (*n* = 33)	HCC group (*n* = 10)	RMS (*n* = 1)	HAS (*n* = 1)	Total (*n* = 45)
Father	17	4	1	1	23 (51.1%)
Mother	10	4			14 (31.1%)
Uncle-aunt	3	2			5 (11.1%)
Grand-parents	2	0			2 (4.4%)
Cousin	1	0			1 (2.2%)
Age at donation (year)					
Median (range)	35 years (24–52 years)	35 years (24–41 years)	38 years	34 years	35 years (24–52 years)
Surgery					
Left lobectomy (SII-III)	30 (90.9%)	6 (60.0%)	1	1	38 (84.4%)
Left hepatectomy (SII-III-IV)	3 (9.1%)	4 (40.0%)			7 (15.6%)
Post-operative complications (Dindo-Clavien score)					
I	29 (87.9%)	10 (100%)	1	1	41 (91.1%)
II	2 (6.1%)				2 (4.4%)
IIIa	1 (3.0%)				1 (2.2%)
IIIb	1 (3.0%)				1 (2.2%)
IV	0				0
V	0				0

of the management of HB, the long-term disease-free survival of HB transplants has improved up to 80%.[24] In 2020, Sindhi et al. estimated that the long-term overall patient survival after transplantation for HB was 82.6%.[25] These rates are consistent with those in our study in which the 5-year survival rate was 87.4%. Over the years, the results in terms of patient survival following LT for HB have improved and were similar between LD and deceased donors with survival rates ranging from 62.5% and 86.7% to 65.5% and 83.3%, respectively.[25,26] With respect to the oncological outcomes in our HB subgroup, the incidence of relapse was 24.2% within the first year post-LT with OS of 50.0% after recurrence. All deaths in this HB series were due to tumor progression despite the early diagnosis of relapse and appropriate treatment. Secondary "rescue" total hepatectomy following the first partial hepatectomy clearly constituted a particular risk factor for relapse after LDLT as was previously demonstrated.[7] Macroscopic or microscopic vascular involvement and microscopic incomplete resection did not influence the risk of relapse, an issue that is still debated.[14,27,28]

In the context of pediatric HCC, Pham et al. reported a long-term disease-free survival rate of 78% at 10 years and OS of 72%.[24] In 2017, Vinayak et al. reported a series of 13 children who underwent transplantation for HCC without satisfying the Milan criteria; of them, five had no recurrence.[29] In the limited series of HCCs presented in their work, LDLT appeared to constitute a valid therapeutic option for as many as 8/10 patients irrespective of the Milan criteria. A recent study, including 150 patients treated for HCC, demonstrated that the survival rate after transplantation for HCC was significantly higher than that after partial liver resection (85.3% vs. 53.5%, respectively), irrespective of the Milan criteria, in pediatric HCC.[25] In our series, in eight HCC cases with underlying liver disease, early detection of a suspect nodule permitted the timely planning of LDLT with a long-term cure in 7/8 of them.

Vascular invasion of the hepatic vein on histology was associated with worse outcomes. In both the HB and HCC groups, all deaths (6/43, 13.9%) were due to tumor relapse. Despite a 53% rate of transplantation from EBV-positive donors in EBV-negative recipients, only one patient who underwent transplantation for RMS died of severe EBV-related stage III-IV lymphoma. The patient who underwent transplantation for unknown HAS received adjuvant chemotherapy and was alive and in complete remission 126 months post-LT.

HB is the most frequent liver malignant tumor in childhood followed by HCC. For HB unresectable through partial hepatectomy, LT was later identified as a valid therapeutic option, taking a place within a "sandwich" approach between neoadjuvant and adjuvant chemotherapy.[7] In parallel to these oncological advances, LT with LD organs was progressively introduced in 1989 following the pioneering series of the University of Chicago.[12] In the pediatric population, using the left liver lobe from LD has permitted to alleviate the shortage of post-mortem donor organs and lower the waiting list mortality in the last 30 years.[30] When analyzing the common benefits expected from LDLT in pediatric recipients, the decrease in mortality on the waiting list, the possibility of improving the clinical and nutritional status of the recipient before LT, and the enhanced graft quality with shorter total ischemic time, all constitute valuable arguments to implement the option of LD within an established pediatric LT program.[30–32] In the particular context of LT for malignant liver tumors, the availability of a liver graft that enables escape from the uncertainty of the post-mortem donor waiting list as well as timely planning of the transplantation as soon as recovery following the last chemotherapy constitutes additional arguments for LDLT. Furthermore, this strategy may contribute to enhancing the overall compliance to oncological protocols including the timing of post-LT chemotherapy.

However, the use of LD in a transplant program requires a particular ethical approach, especially, in children with malignant diseases. At our institution, this approach was centered on the following three main issues: (1) evaluation of the need for LDLT in children with LM; (2) operative risks encountered by LD; and (3) overall and oncological outcomes of LDLT in recipients with LM. Regarding the issue of the need, several organ-sharing organizations, including EuroTransplant, allow the registration of pediatric recipients with LM reaching the end of their neoadjuvant chemotherapy on the high-urgent waiting list with some uncertainty of access to appropriate, size-matched post-mortem organ donor. Furthermore, some centers, including ours, take care of non-resident children for whom access to post-mortem donor waiting list registration is not allowed by the national law, as it is in Belgium. When considering the specific risks of LDLT in children with LM, the first question concerns the putatively increased surgical complication rate considering the technically demanding procedures both in LD and recipients. The 45 donors in this series suffered no mortality and very mild morbidity as evidenced by the Dindo–Clavien categorization of postoperative complications. The selection process for LD is highly selective at our center including the opinion of an independent medical advocate to avoid any additional operative risk and protect the safety and well-being of LD as an absolute priority. Regarding the surgical outcome in recipients, the technical complications encountered did not appear to be increased when compared with those in post-mortem pediatric liver transplants including 0% artery thrombosis despite the small caliber of the donor left hepatic artery. The use of LD internal jugular vein for IVC replacement in the pediatric recipient had no detectable complications in 33 donors whereas thrombosis of the IVC prosthesis was observed in only 3/33 cases, which resolved with heparin therapy. In LDLT, the incidence of biliary complications (leak and stricture) is higher than transplantation by a whole liver deceased donor.[21,30,32] In our series, we reported 8.6% of biliary leak (3/35 cases) and 20% of biliary strictures (7/5 cases). The second ethical concern concerns the benefit/risk ratio in parental LD, a ratio that was high in this series as well as in a larger series of LDLT reported previously from our institution.[21] Nevertheless, extreme caution in the selection of candidate LDs should remain paramount. Finally, this series suggests an encouraging answer to the question of the oncological outcomes of LDLT for LM in children, particularly, those with HB. Validation of the LDLT strategy in other pediatric LM will require comparative multicentric studies.

Since the beginning of the pediatric LT program at CUSL in 1984, 67 children underwent transplantation for LM, and a majority of them (77.6%) involved LD grafts. Accordingly, despite such historical experience in pediatric LT, we were unable to conduct a comparative study between living and deceased donors because the latter were too limited in number (three patients with HB, two with HCC, and three with miscellaneous tumors during the same study period). Nevertheless, we believe that our pilot series contributes to the evaluation of the overall benefit/risk ratio of pediatric LDLT in the context of oncological liver disease. Surgical safety was noted for LD as well as the corresponding pediatric recipients. The use of LDLT for pediatric LM demonstrated encouraging results; however, this approach will require larger studies for validation. The possible identification of a subgroup of HB with an increased risk of tumor recurrence post-LT could constitute a relevant avenue for future research in the field, including the study of the effects of immunosuppression on tumor tolerance.

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CONFLICTS OF INTEREST

None.

AUTHOR CONTRIBUTION

A Pire conceived the study, contributed to data collection and prepared the first draft of the manuscript. R Tambucci contributed to interpretation of data. C de Magnée contributed to data interpretation. E Sokal contributed to interpretation of data. X Stephenne contributed to interpretation of data. I Scheers contributed to interpretation of data. F Zech contributed to interpretation of data and statistical analysis. M Gurevich contributed to data collection. B Brichard contributed to interpretation of data. RR contributed to conceiving the study, to interpretation of data and to revision of further drafts of the manuscript, before the final version. All authors contributed to critically revising the manuscript, approved the final version of the manuscript and the authorship list and take full responsibility for the manuscript.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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