ORIGINAL ARTICLE

An analysis of the outcomes in living donor liver transplantation for pediatric malignant hepatic tumors using nationwide survey data in Japan

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SUMMARY

Malignant hepatic tumors (MHTs) in children are rare and account for approximately 5% of candidates for pediatric liver transplantation (LT) in Japan. We conducted a national survey of pediatric patients undergoing living donor LT for MHTs between October 1990 and April 2018. In total, 116 children underwent LT for MHTs during this study period: 100 hepatoblastomas (HBLs), 10 hepatocellular carcinomas (HCCs), and six other MHTs. The overall patient survival rate at 5 years was 81.3% for HBL, 60.0% for HCC, and 80.0% for other MHTs ($P = 0.047$). In patients with HBL, there was no significant difference in the 1- and 5-year patient survival rates between patients undergoing primary LT and those who received salvage LT for tumor recurrence (89.7%, 81.6% vs. 88.0%, 76%; $P = 0.526$). The 5-year overall survival rate after LT for HBL significantly improved from 63.2% in 1996–2008 to 89.8% in 2009–2018 ($P = 0.018$). The presence of lung metastasis before LT had no significant influence on the long-term survival ($P = 0.742$). Five patients with HCC died, including two who fell outside the Milan criteria. In conclusion, LT for pediatric MHTs, especially HBL, is a valuable treatment option for select patients.

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Key words
live donors, liver, liver clinical, malignancies and long term compliations, pediatric transplantation, solid tumors

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Introduction

Primary pediatric hepatic tumors, regardless of malignancy, are extremely rare and account for about 1–2% of all pediatric tumors [1]. The outcomes of treatment for liver tumors in children have improved dramatically as a result of advances in chemotherapy, radiation therapy, surgery, and liver transplantation (LT).

About three decades have passed since the first living donor LT (LDLT) was conducted in Japan. During this period, LDLT in Japan has developed independently apart from other countries where deceased donors are more commonly accepted. LDLT can make it possible for the patient selection criteria to be tailored to each patient's tumor condition, although the national insurance system only covers the cost for hepatocellular carcinoma (HCC) or hepatoblastoma (HBL) cases [2]. About 5% of pediatric LT cases in Japan are performed for liver tumors, most of which are HBL, and good outcomes have been achieved [3–10]. However, some points concerning the prognosis of LT for malignant hepatic tumor (MHT) remain unclear, including the impact of metastasis before LT on the outcomes, choosing the optimal timing of LT option for patients with advanced MHT, and the outcomes of salvage LT for recurrent tumors.

The present study reviewed the outcomes of pediatric LDLT for MHT according to tumor type derived from a multicenter experience in Japan.

Patients and methods

In Japan, all institutions are required to report the performance of LT to the Japanese Liver Transplantation Society established in 1980. The primary data for all pediatric patients (under 18 years old) undergoing LDLT for MHT in Japan were obtained from the registry kept by the Japanese Liver Transplantation Society. Based on the primary data of the 19 institutions, a more detailed survey was mailed to the 17 institutions that performed LDLT for patients with MHT; only primary data, such as patient outcomes, were available for two patients with HBL and one with HCC.

This study was conducted with the approval of the ethics committee of the National Center for Child Health and Development (No. 2049).

The collected data included patient demographics, tumor stage, neoadjuvant and adjuvant treatment, indication for LT, graft type, surgical data, and survival outcomes. The tumor extent in patients with HBL was described using the PRETEXT and POSTTEXT staging [11]. The candidacy of patients with HCC for LT was evaluated using the Milan criteria [12]. Postoperative complications were graded based on the Clavien–Dindo classification system [13].

Statistical analyses

Fisher's exact test or the chi-square test was used for the comparison of categorical variables, and continuous variables were compared with the Mann–Whitney *U* test. Survival analyses were conducted using the Kaplan–Meier method. The log-rank test was used to detect differences in the survival distributions between tumor categories, and between primary and salvage HBL. Statistical analyses were performed using the SPSS software program, version 22.0 (SPSS Inc., Chicago, IL, USA). A value of $P < 0.05$ was considered to be statistically significant in this study.

Results

One hundred and sixteen LDLT procedures were performed for pediatric MHT in Japan between October 1990 and April 2018, and the cases were followed until December 2019. Among them were 100 cases of LDLT for HBL, 10 for HCC, and six for other MHTs. Figure 1 shows the Kaplan–Meier patient survival curves for all patients, comparing the outcomes for HBL, HCC, and other MHTs. The overall 1-year survival rate for HBL, HCC, and other MHTs was similar at 89.0%, 70.0%, and 100.0%, respectively. However, a significance difference was seen in the 5- and 10-year patient survival

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rates, with respective value of 80.5% and 80.5% seen in the patients with HBL compared with HCC and other malignant tumors ($P = 0.047$; Fig. 1a). The respective 1- and 3-year recurrence-free survival (RFS) rates at were 78.0% and 70.9% for HBL, 60.0% and 60.0% for HCC, and 66.7% and 50.0% for other categories (Fig. 1b). All patients received the induction of immunosuppression consisting of steroid and calcineurin inhibitors (tacrolimus or cyclosporine), with the addition of mycophenolate mofetil in some cases. An mTOR inhibitor was used for maintenance of immunosuppression in three patients.

HBL

Detailed information on the 98 patients with HBL was obtained. The median follow-up period was 6.3 years [interquartile range (IQR), 3.4–11.1 years]. A total of 28 patients (29%) showed tumor recurrence at a median of 6.2 months (IQR, 2.7–12.3 months) after LT (Table 1). Of the 28 patients with tumor recurrence, 11 patients had lung metastasis alone, and 10 patients had ≥2 tumor recurrences sites. The lung was the most common recurrence site (23 patients), followed by the hepatic graft (eight patients) and brain (five patients). The mortality rate in patients with lung metastasis alone was significantly lower than that in patients with extrapulmonary involvement ($P = 0.006$). The 1-, 3-, and 5-year RFS and patient survival rates for all 98 patients were 79.2%, 71.7%, and 70.5% and 89.8%, 85.7%, and 80.9%, respectively. A total of 18 patients died, including 13 of tumor recurrence, two of sepsis, one of bone marrow failure, and two of unknown causes.

Primary LT vs. salvage LT

A total of 68 of the 98 (69.4%) patients received primary LT (PLT). Among these 68 patients, all but 1 with biliary atresia, in whom HBL was incidentally found during the pathological examination of the explanted native liver, received neoadjuvant chemotherapy (NAC). The majority of the patients received the cisplatin-based NAC regimen proposed by the Japanese Study Group for Pediatric Liver Tumor (JPLT) group or International Childhood Liver Tumors Strategy Group (SIOPEL) [14–17]. PLT was indicated in 67 patients as an alternative to aggressive liver resection for the following reasons: (i) a solid tumor involving all four liver sectors after NAC (POSTTEXT IV) in seven patients, (ii) the presence of multifocal tumors across all four liver sectors before or after NAC (PRETEXT IV or POSTTEXT IV) in 44 patients, (iii) a centrally located tumor after NAC (POSTTEXT III) in four patients, (iv) main vascular invasion after NAC (any stage) in 10 patients, (v) tumor progression after NAC from PRETEXT II to POSTTEXT III in one patient, and (vi) an insufficient residual liver volume in one patient.

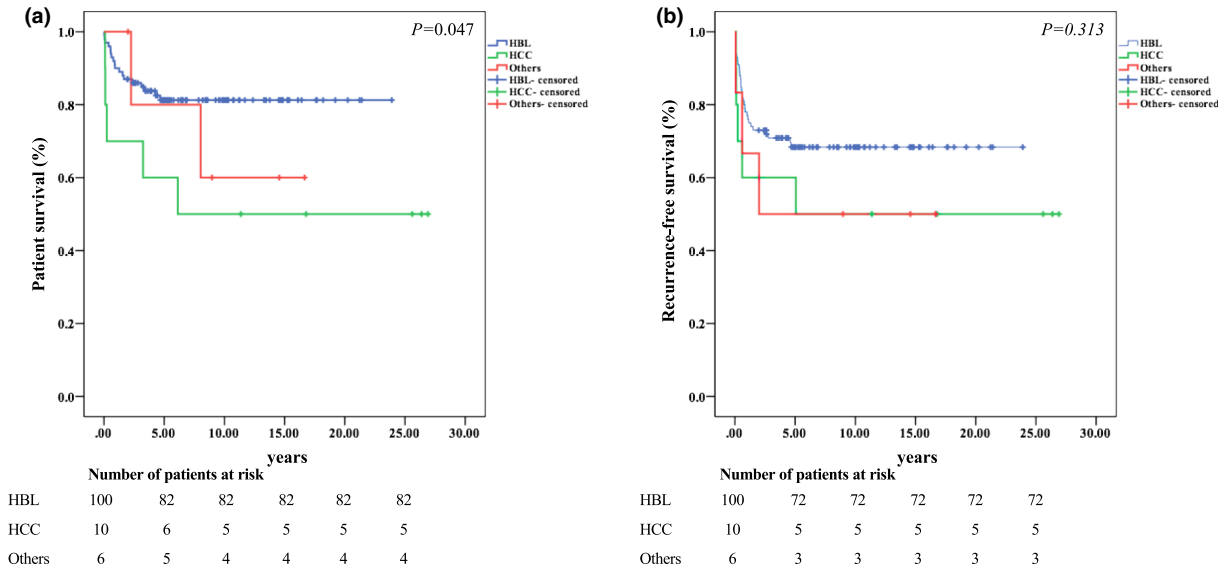

Figure 1 A comparison of the (a) actuarial patient survival and (b) recurrence-free survival of children undergoing pediatric LDLT for MHT. HBL, hepatoblastoma; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; MHT, malignant hepatic tumor.

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Table 1. Diagnostic and treatment features of tumor recurrence after liver transplantation for hepatoblastoma (n = 28).

Type of LT	No.	Age at LDLT (years)	Extrahepatic Lesion at diagnosis	Extrahepatic Lesion at LDLT	AFP at LDLT (ng/ml)	Interval LT/recurrence (months)	Lung metastasis (times)	Nonpulmonary recurrence	Treatment for metastases	Residual metastasis	Outcome (f/u year)	Cause of death
Primary	1	0.8	No	No	4390	4.7	Yes (1)	Skin	CTX	Lung, skin	Died (0.6)	Recurrence
	2	1.1	No	No	1 061 480	15.9	No	Graft, PC	CTX, surgery	PC	Died (1.6)	Recurrence
	3	1.5	No	No	67 078	4.5	No	Diaphragm	CTX, surgery	None	Died (0.9)	BM failure
	4	1.8	Lung	Lung	1 950 000	0.5	Yes (1)	Brain	CTX, surgery	Brain	Died (0.8)	Recurrence
	5	2.4	Lung	Eradicated	331	5.5	Yes (1)	None	CTX, surgery	None	Alive (11.3)	–
	6	2.6	Lung	Lung	5514	18.0	Yes (3)	None	CTX, surgery	None	Alive (2.8)	–
	7	2.6	Stomach	Stomach	5749	2.5	Yes (1)	None	CTX	Lung	Died (0.9)	Recurrence
	8	3.1	Lung	Lung	9475	12.1	Yes (4)	None	CTX, surgery	None	Alive (6.4)	–
	9	3.1	Lung	Eradicated	2336	2.8	Yes (1)	None	CTX, surgery	None	Alive (5.2)	–
	10	3.5	No	Lung	4	0.8	Yes (1)	Graft	CTX	Graft, lung	Died (0.1)	Recurrence
	11	3.6	No	No	61 950	4.2	Yes (1)	None	CTX, surgery	None	Alive (13.8)	–
	12	3.7	No	No	331 801	1.7	Yes (6)	Bone, LN	CTX, surgery, RFA, radiation	Bone	Died (4.3)	Recurrence
	13	3.8	Lung	Eradicated	153 355	12.9	Yes (1)	None	CTX, surgery	None	Alive (3.3)	–
	14	4.6	Lung	Lung	42 591	7.0	Yes (1)	None	CTX, surgery	None	Alive (1.9)	–
	15	4.7	No	No	1 175 690	9.9	Yes (1)	None	CTX, surgery	None	Alive (15.2)	–
	16	6.6	No	No	3330	6.4	Yes (4)	None	CTX, surgery	None	Died (1.5)	Sepsis
	17	7.1	No	No	21 938	10.1	No	Graft, PC	CTX	Graft, PC	Died (1.3)	Recurrence
	18	8.1	Lung	Eradicated	206 269	6.9	Yes (1)	None	CTX, surgery	None	Alive (9.8)	–
	19	9.6	Lung	Lung	1073	0.9	Yes (2)	Brain	CTX, surgery	Brain	Died (0.6)	Recurrence
Salvage	1	2.2	No	Lung	1 238 630	1.4	Yes (1)	Brain, graft	CTX, surgery	Brain, graft, lung	Died (0.4)	Recurrence
	2	2.9	Lung	Lung	11 603	5.9	No	Brain	CTX, surgery radiation	None	Alive (6.5)	–
	3	3.9	No	No	170 910	0.8	Yes (1)	Graft	CTX	Graft, lung	Died (0.5)	Recurrence
	4	5.3	Colon	Colon	8800	6.0	Yes (1)	Graft, PC	CTX, surgery	Graft	Died (3.1)	Recurrence
	5	7.5	No	No	54 700	33.1	Yes (1)	Diaphragm, graft	CTX, surgery	Graft, lung	Died (3.4)	Recurrence
	6	7.9	No	No	13 038	8.2	Yes (1)	Brain	CTX, surgery	Brain	Died (2.4)	Recurrence
	7	9.4	No	No	10	55.0	No	Graft	CTX, surgery	None	Alive (8.4)	–
	8	11.9	No	Lung	6	13.7	Yes (1)	LN	CTX, surgery	None	Alive (2.5)	–
	9	16.9	No	No	33	31.3	No	Diaphragm	CTX, surgery	None	Alive (5.3)	–

AFP, alpha-fetoprotein; BM, bone marrow; CTX, chemotherapy; LDLT, living donor liver transplantation; LN, lymph node; LT, liver transplantation; PC, peritoneal carcinomatosis; PLT, primary liver transplantation; SLT, salvage liver transplantation.

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A total of 30 of 98 (30.6%) patients received salvage liver transplantation (SLT), including 25 patients for recurrent tumor (SLT group A) and five patients for deteriorating liver function after liver resection (SLT group B). Of the 30 patients undergoing SLT, 11 underwent liver resection 2 or 3 times. The types of liver resections included right trisectionectomy ($n = 14$), right hepatectomy ($n = 5$), left trisectionectomy ($n = 3$), left hepatectomy ($n = 3$), right anterior sectionectomy ($n = 1$), right posterior sectionectomy ($n = 1$), left lateral segmentectomy ($n = 2$), and nonanatomical tumor resection ($n = 15$). Two patients did not receive chemotherapy before liver resection; transcatheter arterial embolization was used in one patient with PRETEXT I before liver resection and the other patient with PRETEXT III underwent liver resection without any treatment before surgery.

More than half of the patients (59.4%) received irinotecan (CPT 11) as adjuvant chemotherapy (ACT). Forty-five of the 68 patients undergoing PLT received ACT with a median two cycles (IQR, 1–3 cycles). ACT was started at a median of 29 days (IQR, 26–39 days) after LT. Twenty-one of the 30 patients undergoing SLT received ACT after LT with a median two cycles (IQR, 1–3 cycles); most of them (20 patients) were in SLT group A. ACT was started at a median of 35 days (IQR, 29–51 days) after LT.

The demographic profiles of these patients are shown in Table 2. The serum levels of alpha-fetoprotein (AFP) at the time of the diagnosis and before LT were significantly higher in patients undergoing PLT than in others (at the time of the diagnosis, $P = 0.049$; before LT, $P = 0.002$). Patients undergoing PLT showed a more progressive tumor stage at the time of the diagnosis than others ($P < 0.001$). Patients undergoing PLT were more likely to have vascular thrombus, including PV thrombus, than others (at the time of diagnosis, $P = 0.049$; before LT, $P = 0.105$). Comparing patients in the PLT and SLT group A, the PLT patients were more likely to have metastatic disease to the lungs at the time of the diagnosis than the SLT patients ($P = 0.029$). All 5 patients requiring SLT for a

Table 2. Demographic profiles of primary and salvage liver transplantation for hepatoblastoma.

	PLT ($n = 68$)	SLT group A ($n = 25$)	SLT group B ($n = 5$)	*P* value
At the time of diagnosis				
AFP	551 925 (197 029–1 114 250)	144 912 (7869–676 990)	593 820 (143 838–757 200)	**0.049**
PRETEXT stage I/II/III/IV	0/2/15/51	1/5/11/8	1/0/4/0	**<0.001**
Lung metastasis	21 (31)	2 (8)	1 (20)	0.067
PV tumor thrombus	12 (18)	0	0	**0.049**
IVC tumor thrombus	3 (4)	0	0	0.510
Before LT				
AFP	3797 (42 527 101)	1411 (39–20 378)	6 (4–44)	**0.002**
POSTTEXT stage* I/II/III/IV	0/3/16/49	NA	NA	NA
Lung metastasis	13 (19)	2 (8)	1 (20)	0.426
PV tumor thrombus	9 (13)	0	0	0.105
IVC tumor thrombus	2 (3)	0	0	0.637
Surgical information and outcome				
Operation time (min)	602 (477–719)	682 (530–893)	732 (556–930)	0.141
Blood loss (ml/kg)	45 (30–68)	38 (22–58)	73 (67–114)	0.112
GRWR (%)	2.21 (1.75–2.62)	1.55 (1.22–2.00)	2.62 (1.44–2.77)	**<0.001**
Surgical complication	20 (29)	13 (52)	1 (20)	0.099
Infection	14 (20)	6 (24)	3 (60)	0.133
TCMR	15 (22)	9 (36)	3 (60)	0.102
Recurrence, *n* (%)	19 (28)	8 (32)	1 (20)	0.845
Mortality, *n* (%)	12 (18)	6 (24)	0	0.432
Death due to recurrence, *n* (%)	10 (15)	5 (20)	0	0.509

Bold values indicate statistical significance.

AFP, alpha-fetoprotein; GRWR, graft-to-recipient weight ratio; HBL, hepatoblastoma; IVC, inferior vena cava; LT, liver transplantation; NA, not applicable; PLT, primary liver transplantation; SLT, salvage liver transplantation; TCMR, T cell-mediated rejection; PV, portal vein.

*POSTTEXT staging was available in 58 patients.

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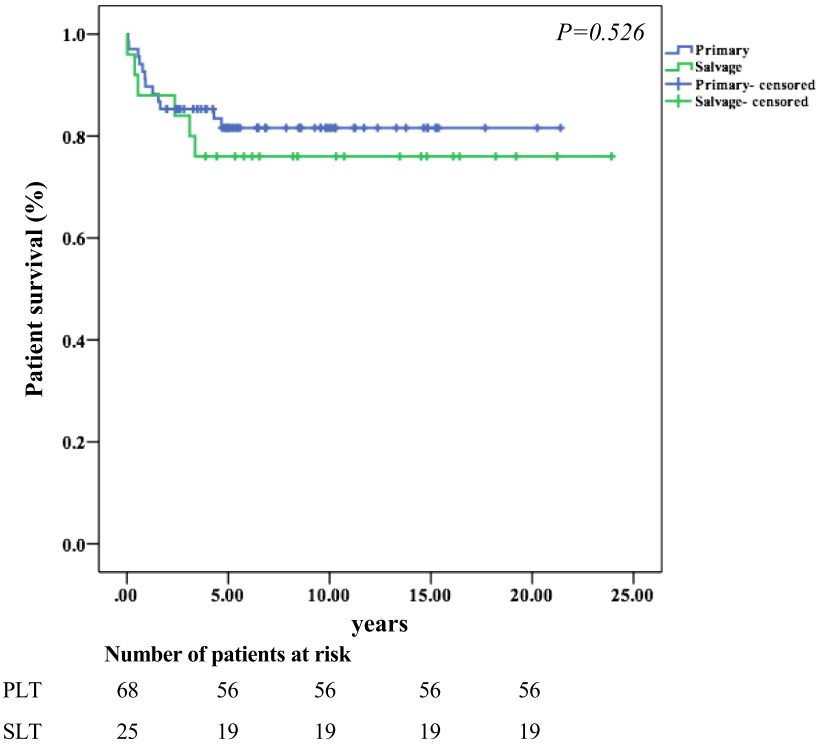

Figure 2 A comparison of the actuarial patient survival of HBL children undergoing PLT and SLT for tumor recurrence. HBL, hepatoblastoma; PLT, primary liver transplantation; SLT, salvage liver transplantation.

deteriorating liver function after liver resection remained alive. Figure 2 shows the Kaplan–Meier patients' survival curves for HBL, comparing the outcomes of PLT and SLT patients in group A. The 1-, 3-, and 5-year overall survivals for the 68 patients were 89.7%, 85.3%, and 81.6% compared with 88.0%, 84.0%, and 76.0%, respectively, for the 25 SLT patients in group A ($P = 0.526$). In SLT patients in group A, the AFP levels before LT were significantly higher in non-survivors than in survivors ($P = 0.004$).

Among the tumor factors contributing to tumor recurrence analyzed in PLT patients and SLT patients in group A based on previous results, the serum AFP level at the time of the diagnosis and serum AFP level at LT were significant in PLT patients ($P = 0.007$, $P = 0.029$), while extrahepatic lesion before LT was an independent predictor in SLT patients ($P = 0.024$) according to a univariate analysis (Table 3) [3].

Analyses of patients with lung metastasis

Of the 68 patients who received PLT, 21 had lung metastases (Fig. 3). Among these 21 patients, complete radiographic clearance of lung metastases was achieved in 10 at the time of LT, while the remaining 11 required metastasectomy before LT. New lesions appeared in the lungs of two patients during NAC. On comparing the prognosis by the presence of lung metastases at various stages, the recurrence rate was significantly worse in the patients with lung metastases at the time of the diagnosis than in those without lung metastases ($P = 0.043$), whereas there was no marked difference in the mortality rate ($P = 0.742$). The mortality rate tended to be higher in patients with the appearance of lung metastasis during NAC than in others; however, the difference did not reach statistical significance ($P = 0.086$).

Trends in the survival of patients undergoing PLT

The era of transplant for HBL was analyzed to further address whether or not the timing of LT was associated with the survival. Starting in April 2008, the costs of LT for HBL were covered by the national health insurance system in Japan. The patients undergoing PLT were divided into two groups based on the year of LT, up to 2008 and 2008 and later. Patients in 2008 and later had more advanced tumors (i.e. more progressive tumor stage and high rate of lung metastasis and main vascular invasion) at the time of the diagnosis than those

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Table 3. Factors affecting recurrence-free survival after primary and salvage LT for HBL.

	Primary LT			Salvage LT		
Variable	Total	Recurrence *n* (%)	*P* value	Total	Recurrence *n* (%)	*P* value
AFP at diagnosis						
<500 000 ng/ml	33	4 (12.1)	**0.007**	14	4 (28.6)	0.695
≥500 000 ng/ml	35	15 (42.9)		11	4 (36.4)	
PRETEXT staging						
II	2	0	0.677	6	4 (66.7)	0.051
III	15	4 (26.7)		11	1 (9.1)	
IV	51	15 (29.4)		8	3 (37.5)	
Extrahepatic lesion at diagnosis						
Yes	21	9 (42.9)	0.084	5	2 (40)	0.668
No	47	10 (21.3)		20	6 (30)	
Vascular involvement at diagnosis						
Yes	35	13 (37.1)	0.107	3	1 (33.3)	0.958
No	33	6 (18.2)		22	7 (31.8)	
AFP before LDLT						
<4000 ng/ml	34	5 (14.7)	**0.029**	14	2 (14.3)	0.081
≥4000 ng/ml	34	14 (41.2)		11	6 (54.5)	
POSTTEXT staging						
II	3	0	0.464	–	–	NA
III	16	5 (31.3)		–	–	
IV	49	14 (28.6)		–	–	
Extrahepatic lesion before LDLT						
Yes	13	6 (46.2)	0.166	3	3 (100)	**0.024**
No	55	13 (23.6)		22	5 (22.7)	
Vascular involvement before LDLT						
Yes	35	13 (37.1)	0.107	–	–	NA
No	33	6 (18.2)		–	–	
Chemotherapy after LDLT						
Yes	54	16 (29.6)	0.742	20	8 (40)	0.140
No	14	3 (21.4)		5	0	

Bold values indicate statistical significance.

AFP, alpha-fetoprotein; HBL, hepatoblastoma; LDLT, living donor liver transplantation; LT, liver transplantation; NA, not assessed.

encountered up to 2008, while the serum AFP levels at LT were significantly lower in patients encountered in 2008 and later ($P < 0.05$; Table 4). The AFP ratio, which described the rate of change in AFP by comparing the values at the diagnosis and before LT, was significantly lower in patients encountered up to 2008 than in those encountered later ($P = 0.023$). The 1- and 5-year patient survival was significantly better in patients who received LT in 2008 and later than in those treated up to 2008 (91.8%, 89.8% for patients in 2008 and later vs. 84.2%, 63.2% for patients up to 2008; $P = 0.018$), while no significant difference was seen in the RFS ($P = 0.083$; Fig. 4). There was a significant difference in the mortality between recurrence patients who received LT in 2008 and later and those who received it up to 2008 ($P = 0.023$).

HCC

Detailed information on the nine patients with HCC was obtained in this study (Table 5). Six of the nine patients had underlying liver disease (biliary atresia, $n = 4$; Alagille syndrome, $n = 1$; mitochondrial hepatopathy, $n = 1$), and in five of them, the tumor was discovered incidentally from the explanted native liver. One patient was initially diagnosed with HBL but eventually diagnosed with HCC from the explanted native liver. Aside from that one patient, all patients received neither NAC nor treatment via the hepatic artery nor chemotherapy before LT. Two patients with multiple lesions fell outside the Milan criteria at the time of LT, including one incidentally diagnosed case and another diagnosed with HBL. One patient with mitochondrial

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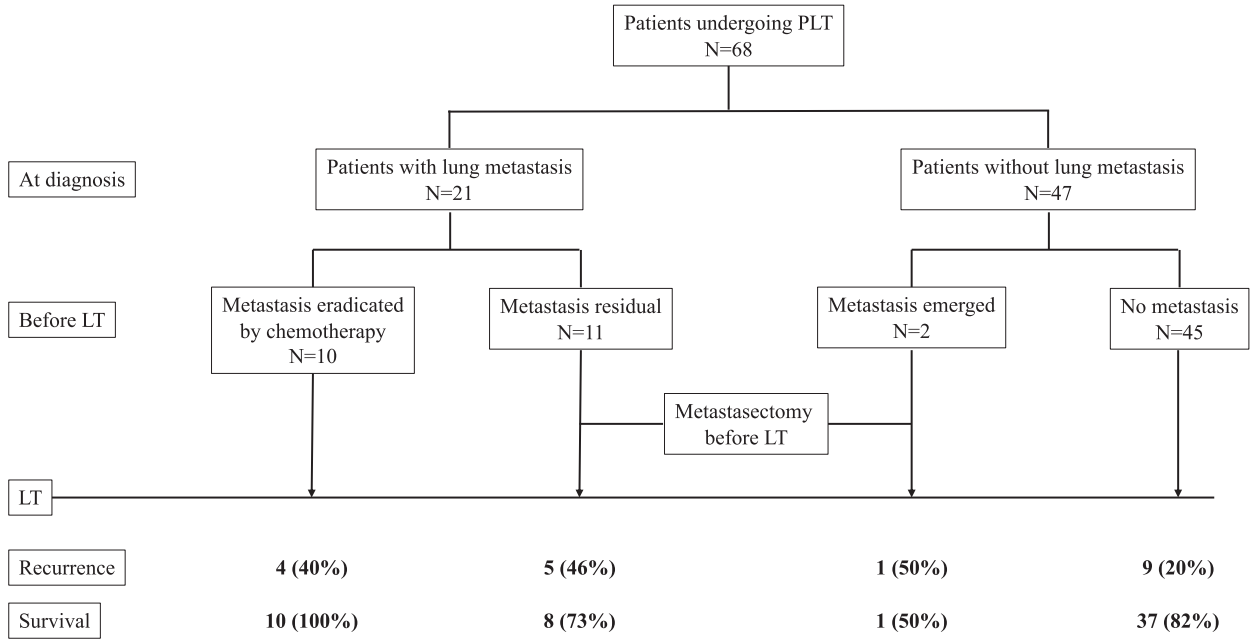

Figure 3 Flowchart of the status of lung metastasis in patients with HBL. HBL, hepatoblastoma; LT, liver transplantation; PLT, primary liver transplantation.

Table 4. Demographic profiles of primary liver transplantation for hepatoblastoma based on the era of liver transplantation.

	Up to 2008 (*n* = 19)	2008 and later (*n* = 49)	*P* value
At the time of diagnosis			
AFP (ng/ml)	699 700 (252 620–1 250 000)	473 172 (156 872–1 114 750)	0.362
PRETEXT stage I/II/III/IV	0/0/9/10	0/2/6/41	**0.006**
Lung metastasis	1 (5)	20 (41)	**0.004**
PV tumor thrombus	2 (11)	10 (20)	0.487
IVC tumor thrombus	0	3 (6)	0.554
Before LT			
AFP (ng/ml)	7040 (3710–64 514)	2052 (334–12 439)	**0.034**
AFP ratio (%)	2.6 (0.8–35.1)	0.4 (0.1–4.2)	**0.023**
POSTTEXT stage* I/II/III/IV	0/0/9/10	0/3/7/39	**0.012**
Lung metastasis	1 (5)	12 (24)	0.092
PV tumor thrombus	1 (5)	8 (16)	0.427
IVC tumor thrombus	0	2 (4)	0.925
Surgical information and outcome			
Operation time (min)	690 (527–752)	582 (466–701)	0.104
Blood loss (ml/kg)	67 (36–123)	39 (24–65)	**0.036**
Surgical complication	9 (47)	11 (22)	0.073
Infection	1 (5)	13 (27)	0.091
TCMR	4 (21)	11 (22)	0.901
Recurrence, *n* (%)	8 (42)	11 (22)	0.135
Mortality, *n* (%)	7 (37)	5 (10)	**0.028**
Death due to recurrence, *n* (%)	6 (32)	4 (8)	**0.023**

Bold values indicate statistical significance.

AFP, alpha-fetoprotein; HBL, hepatoblastoma; IVC, inferior vena cava; LT, liver transplantation; NA, not applicable; TCMR, T cell-mediated rejection; PV, portal vein.

*POSTTEXT staging was available in 58 patients.

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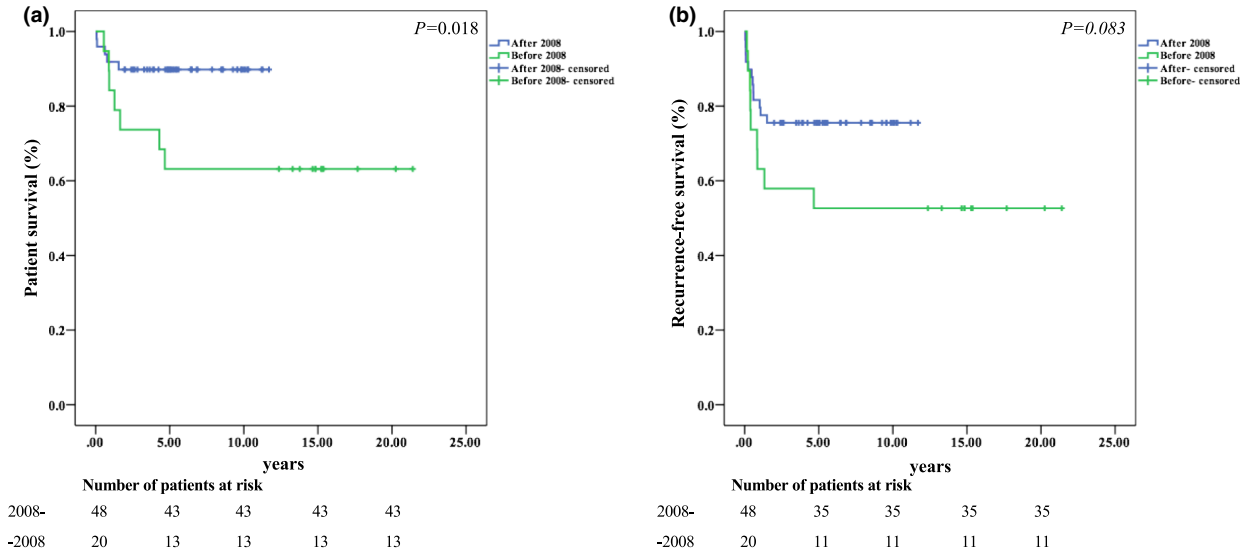

Figure 4 Temporal trends in the (a) actuarial patient survival and (b) recurrence-free survival in LT before and after medical coverage of LT for HBL. HBL, hepatoblastoma; LT, liver transplantation.

hepatopathy underwent SLT for recurrent HCC after nonanatomical liver resection. Transplant-related complications had occurred in five patients, including TCMR in two patients, infection in two patients, intraabdominal abscess in one patient, and biliary stricture in one patient. Three patients had tumor recurrence in the graft, lungs, and lymph nodes at 1.0 months, 7.2 months, and 5.1 years, respectively. Two patients were placed in palliative care as a result of multiple metastases, and the remaining one was unable to undergo complete resection as a result of multiple lymph node metastases despite an attempt to perform lymphadenectomy. A total of five patients died, including three of recurrence/metastatic disease, one of infection, and one of respiratory disorder. Both patients who fell outside the Milan criteria died of tumor recurrence. One patient undergoing SLT died within three months after LT as a result of respiratory disorder.

Other MHTs

Six patients underwent LT for liver tumors other than HBL and HCC: hepatic epithelioid hemangioendothelioma (HEH), $n = 2$; incidental finding of cholangiocellular carcinoma, $n = 1$; undifferentiated embryonal sarcoma (UES), $n = 1$; infantile choriocarcinoma, $n = 1$; metastatic liver tumor from solid pseudopapillary tumor of the pancreas, $n = 1$ (Table 5). The patient with cholangiocellular carcinoma had received LT for biliary atresia, and a tumor was found incidentally from the explanted native liver. The most common indication for LT was unresectable tumor, but one patient with infantile choriocarcinoma received urgent LT as a result of tumor rupture. Postoperative complications were seen in three patients. One patient with HEH had hepatic arterial thrombosis that did not require surgical intervention. One patient each with HEH, UES, and infantile choriocarcinoma had tumor recurrence, and 2 of them died as a result of uncontrollable tumor recurrence at 2.2 and 8.1 years.

Discussion

Thus far, reports based on national and single-center experiences have described outcomes after LT for all pediatric MHTs. Multicenter trials and international collaboration between pediatric oncology groups have led to significant improvements in the long-term outcomes of pediatric MHTs during the last three decades, and LT has firmly established itself as a treatment option for unresectable hepatic tumors [18–22]. Furthermore, the implementation of LDLT has allowed to provide optimal timing of surgical intervention for patients with MHTs, particularly those with HBL, which requires timely LT following recovery after the last NAC course and metastasectomy [3,10,23].

Our excellent results of patients with HBL in this survey are compatible with those of recent single- and multicenter reports of LT for advanced HBL, with survival rates exceeding 80% [18–20]. In Japan, medical coverage of LT for HBL was not approved until April 2008, and our own protocols (JPLT-1 and JPLT-2) did

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Table 5. Patient and tumor characteristics of 14 other malignant hepatic tumors.

Type of tumor	No.	Age at LDLT (years)	Underlying liver disease	Diagnosis	Pretransplant treatment	Tumor status at LT	Extrahepatic lesions at LT	Chemotherapy after LT	Complications	Recurrence	Outcome (f/u year)	Cause of Death
HCC	1	1.9	–	Pretransplant	No	Within Milan	None	No	CMV, pneumonia, TCMR	No	Died (0.1)	CMV
	2	4.5	AGS	Incidental	No	Within Milan	None	Epirubicin	Biliary stricture	No	Alive (16.8)	–
	3	6.3	MRCD	Pretransplant	Liver resection	Salvage	None	No	Respiratory infection	No	Died (0.2)	Respiratory disorder
	4	7.7	BA	Incidental	No	Within Milan	None	No	None	No	Alive (26.9)	–
	5	8.2	BA	Incidental	No	Beyond Milan	None	No	Convulsion	LN	Died (6.1)	Recurrence
	6	9.5	HBL s/o	Incidental	CTX	Beyond Milan	None	No	TCMR	Graft	Died (0.1)	Recurrence
	7	11	BA	Incidental	No	Within Milan	None	Uracil/tegafur	None	No	Alive (25.6)	–
	8	12.3	BA	Incidental	No	Within Milan	None	No	Intraabdominal abscess, TCMR	No	Alive (11.4)	–
	9	13.9	–	Pretransplant	No	Within Milan	None	No	None	Lung	Died (3.2)	Recurrence
HEH	1	0.3	–	Pretransplant	CTX	Multiple	None	No	CMV, HAT	No	Alive (9.0)	–
	2	4.1	–	Pretransplant	CTX	Multiple	None	No	None	Graft, lung	Died (2.2)	Recurrence
CCC	1	17.8	BA	Incidental	No	NA	None	No	TCMR	No	Alive (16.7)	–
USE	1	15.3	–	Pretransplant	CTX	Multiple	None	VAC, Hi-MEC	None	Intra abdomen	Died (8.0)	Recurrence
ICC	1	0.3	–	Pretransplant	No	Rupture	None	JEB	CMV	Lung	Alive (2.0)	–
MET	1	14.3	–	Pretransplant	No	Multiple	None	No	None	No	Alive (14.6)	–

AGS, Alagille syndrome; BA, biliary atresia; CCC, cholangiocellular carcinoma; CMV, cytomegalovirus; CTX, chemotherapy; HAT, hepatic artery thrombosis; HCC, hepatocellular carcinoma; HEH, hepatic epithelioid hemangioendothelioma; Hi-MEC, ifosfamide, etoposide, carboplatin, and melphalan; ICC, infantile choriocarcinoma; JEB, carboplatin, etoposide, and bleomycin; LDLT, living donor liver transplantation; LN, lymph node; LT, liver transplantation; MET, metastatic liver tumor; NA, not applicable; TCMR, T cell-mediated rejection; USE, undifferentiated embryonal sarcoma; VAC, vincristine, dactinomycin, and cyclophosphamide.

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not include the guidelines for LT as a treatment option. With the widespread acceptance of LT as a lifesaving option for unresectable HBL and the establishment of a system for early consultations with a transplant center, the recent outcomes might have significantly improved.

In the current study, the 5-year overall survival after LT for HBL remarkably improved from 63.2% in the period up to 2008 to 89.8% in the most recent decade, whereas RFS demonstrated similar findings. Given that the cases encountered more recently had more advanced tumors, the recent multidisciplinary efforts for the management of HBL might have contributed to the improved outcomes. As our own multicenter protocol (JPLT-1 and JPLT-2) did not include a guideline for LT in patients with unresectable HBL up to 2008, patients were likely to receive high-dose chemotherapy according to each center's discretion and some of them underwent LT with an inadequate chemotherapy response or poor chemosensitivity. Many institutions were able to manage the patients with unresectable HBL according to the surgical guidelines including LT as a treatment option after 2008. The situation likely influenced the difference in the patient survival rate between up to 2008 and 2008 and later, although the RFS showed similar findings. The ongoing JPLT-3 protocol study, which includes surgical guidelines from SIOPEL, defines LT for HBL as follows: any PRETEXT IV hepatoblastoma and unifocal, centrally located tumors involving main hilar structures or main hepatic veins that is unlikely to become tumor-free even after a good response to chemotherapy [24]. However, there is still no consensus among oncologists and surgeons concerning the management of patients with the following status; lung metastasis before LT, SLT for tumor recurrence, or recurrence of multiple metastases after LT.

Given the current debate concerning the expanded indications of LT for HBL patients with lung metastases, patients need to be assessed on an individual level. Given our finding that the number of patients with lung metastases increased after insurance coverage, if complete radiographic clearance can be achieved, then the presence of lung metastasis before LT has no significant influence on the long-term patient survival, although the presence of lung metastasis at the time of the diagnosis remains a significant risk factor for tumor recurrence. Another recent report also showed that the presence of lung metastases at the diagnosis, if resolved before LT, did not influence the outcomes [25]. However, careful management and assessments are still required in patients who develop new lesions during NAC, even if the lesions are resectable, as the recurrence and mortality rates were shown to be high in such patients in the present study.

As a result of the lack of clear criteria concerning the indication of LT for HBL, the position of SLT in patients who have relapsed is another issue that needs to be resolved. An initial review of global experiences showed unsatisfactory outcomes of SLT for tumor recurrence. Otte et al. reported that patients who received SLT showed significantly worse outcomes (30%) than patients who underwent PLT (82%) after a 6-year follow-up [26]. In contrast, the current study found no significant difference in the patient survival between patients who received PLT and those who received SLT for tumor recurrence, similar to our previous report [3]. The report by Otte et al. is more than a decade old, and it may be a good time to review the outcomes of SLT for recurrent tumors. Some studies have suggested the feasibility of resection for advanced HBL, with excellent OS rates of 80–88% reported [27,28]. Because the influence of long-term immunosuppression or the development of secondary malignancies is uncertain, aggressive liver resection may be a better treatment option than LT for advanced HBL. In addition, our results showed that SLT patients with high serum levels of AFP at LT had a higher mortality rate than those with low levels. Therefore, the choice of LT as a treatment for such patients should be made carefully. Most importantly, an appropriate strategy is needed to avoid SLT. However, it is difficult to draw any definitive conclusions about SLT for tumor recurrence in the current situation as the population of patients who demonstrated recurrence after aggressive liver resection but were not suitable for LT was not thoroughly evaluated in this study.

The usual recurrence site of HBL after LT is the lung, while nonpulmonary recurrence, including the brain as well as grafts, bones, and diaphragm, is uncommon. Although published data on the outcomes of relapsed patients after LT are limited, previous reports have documented the poor prognosis of patients with nonpulmonary metastases [29]. In the present study, the prognosis of patients with lung metastasis and nonpulmonary involvement was worse than that of patients with lung metastasis alone. Consequently, one patient with brain metastasis and recurrence in graft remains alive. Our colleague recently reported a patient with recurrence in a transplanted liver which was the first successful case of re-LDLT for recurrent HBL [30]. The patients achieved complete eradication of peritoneal metastases under indocyanine green (ICG) fluorescence imaging. There have also been several reports of navigation surgery using ICG to detect small metastatic HBL, which has likely contributed to the improved outcomes

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in recent years among patients with lung metastases as well as in recurrent patients [31–33].

Although there are some reports of LT for HCC in children with recent improvements in outcomes, experience is limited as a result of the rarity of HCC among pediatric populations [19,34,35]. A recent analysis from the United States showed that the 5-year overall survival after LT dramatically improved from 60% in the period before 2010 to 81% in the most recent decade [20]. Our study included only nine patients with HCC, and the results were less satisfactory than in these previous reports. Half of the six HCC patients with an underlying liver disease died, although the cause of death was non-recurrence-related complications, such as infections or respiratory disorders. Previous reports have described excellent survival outcomes after LT for incidental HCC and HCC with preexisting liver disease, especially in cases of inherited metabolic liver disease, as regular liver screening and the early detection of suspicious HCC nodules were shown to prompt surgical therapy with a more favorable prognosis, particularly in the pediatric populations [19,36]. Of the nine patients with HCC in the present study, two fell outside the Milan criteria, and both died from tumor recurrence. In cases of adult LT, many centers have proposed expanded criteria for HCC and found that these criteria expand the patient selection beyond the Milan criteria without worsening the overall outcomes [37–40]. Even in pediatric series, some patients who fell outside the Milan criteria benefited from LT [19]. However, the low numbers of patients with HCC in this study prohibit us from making any meaningful inference concerning the risk of recurrence based on patient characteristics.

The outcomes of LT for pediatric MHT other than HCC and HBL are poorly understood because of the rarity of this entity. LT is a potential alternative for these patients with large tumors that are deemed unresectable, tumors adjacent to vital anatomical structures, and those refractory to treatment. Although HEH has been reported in children younger than 15 years old, the outcomes of pediatric LT were dismal, with overall and graft survival rates at 5 years post-transplant of 60% and 50%, respectively [19,41]. In contrast, in UES cases, despite the aggressive nature of this childhood liver tumor, recent data suggested positive outcomes for children who undergo either surgical resection alone or a combination of resection and chemotherapy [18,19,21,42]. In LT for other rare liver malignancies, there are few studies available in children, and data are mostly in the form of case reports or single-center experiences [19,43–46]. While the number of cases included in the present study is limited, pediatric LT for these MHTs can be considered reasonable based on our experience.

In conclusion, LDLT allows for the optimal timing of LT, given the absence of any delay between the completion of chemotherapy and elective LT, which is a valuable treatment option for select patients with unresectable pediatric MHTs. In particular, the outcomes of patients undergoing LDLT for HBL are comparable to those for cases of nonmalignant disease. In addition, we recently introduced LT for patients with more advanced disease, such as lung metastasis, and observed good outcomes. However, corroborating reports from other groups are needed to verify these findings as a result of the rarity of unresectable pediatric MHTs.

Authorship

HU: designed the study and wrote the manuscript. SS, MK, YU, SM, HH, HO, SE, YT, KU, NK, HE, SU and HO: designed the study and revised the manuscript.

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Conflict of interest

None of authors have any conflict of interest to declare concerning the present manuscript. This work was supported in part by the grant of National Center for Child Health and Development (27-1), Japan.

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