score was 16.3 ± 8.2 (3–37) (Table 2). The initial regimen of immunosuppression consisted of tacrolimus and steroids in 91.8% of the cases.

Patient survival

The one-, five-, 10-, and 15-yr patient and graft survival rates of the patients with metabolic disorders undergoing LDLT were 91.2%, 87.9%, 87.0%, and 79.3%, and 91.2%, 87.9%, 86.1%, and 74.4%, respectively. There were no statistical differences in the patient or graft survival rates in the study population ($p = 0.187$; Fig. 2). When the data were analyzed separately, there were distinct differences in outcomes based on the original liver disease. In this study, patients with urea cycle disorder and Wilson's disease exhibited a significantly better patient survival, with 15-yr rates of 96.1 and 77.6% ($p < 0.001$; Fig. 3).

Recipient and donor factors were analyzed with respect to overall recipient survival. The results of the univariate and multivariate analyses are shown in Table 3. According to the univariate analysis, the etiology of liver disease and transplant era were significant predictors of survival. The univariate analysis of the factors predicting patient survival showed no significant associations between survival and donor age, sex, gender combination, relationship of the donor, ABO compatibility, graft type, or recipient age and sex. Factors with $p < 0.1$ were included in the multivariate analysis, and the etiology of liver disease and transplant era were found to be significant predictors of overall survival. Significant improvements in patient survival were obtained within the recent five yr, with one- and five-yr patient survival rates of 94.5 and 89.9%, respectively ($p < 0.001$; Fig. 4).

Original liver disease

When the data were analyzed according to the original liver disease, differences were found in each metabolic disease (Table 4). Wilson's disease was diagnosed at a median age of 11.0 ± 4.4 (range: 6–17) yr. The diagnosis was made based on laboratory data and clinical findings (the serum ceruloplasmin, urinary copper excretion and hepatic copper concentrations, and presence of Kayser–Fleischer rings) in all cases, as ATP7B genetic examinations were performed in the most recent nine cases. Four patients had an affected

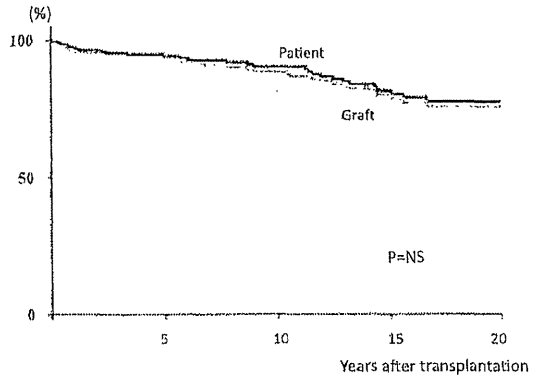

Fig. 2. Patient and graft survival after LDLT.

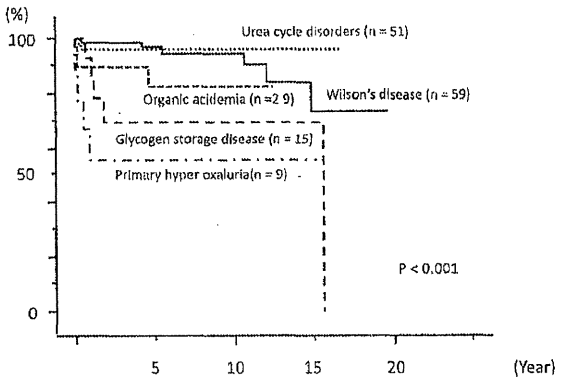

Fig. 3. Patient survival according to the original liver disease.

Table 3. Factors associated with long-term survival after LDLT for metabolic disorders

	Hazard Ratio	95% confidence interval		p-Value
Univariate analysis				
Donor age groups	1.880	0.853	4.145	0.117
Donor sex	0.809	0.548	1.194	0.285
Gender combination	0.889	0.623	1.269	0.519
Donor relationship to recipient	1.129	0.749	1.702	0.562
Donor ABO status	1.047	0.722	1.519	0.809
ABO compatibility	1.201	0.737	1.955	0.462
Graft type	0.967	0.522	1.794	0.916
Recipient age group	1.186	0.857	1.640	0.303
Recipient age: ≥1 yr vs. <1 yr	1.186	0.446	3.153	0.732
Recipient sex: male vs. female	1.090	0.738	1.608	0.666
Original disease	1.151	1.067	1.243	0.000
UCD vs. others	0.230	0.054	0.976	0.046
Wilson's disease vs. others	0.133	0.018	0.980	0.048
Wilsonian fulminant vs. others	1.847	0.631	5.400	0.263
Primary hyperoxaluria vs. others	4.561	1.566	13.282	0.005
Transplant era	0.599	0.403	0.889	0.011
Multivariate analysis (stepwise forward selection method)				
Original disease	1.179	1.089	1.276	<0.001
UCD vs. others	–	–	–	0.664
Wilson's disease vs. others	–	–	–	0.108
Primary hyperoxaluria vs. others	–	–	–	0.142
Transplant era	0.594	0.409	0.863	0.006

UCD, urea cycle deficiency.

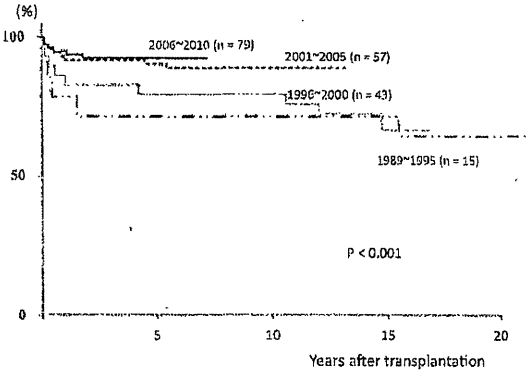

Fig. 4. Patient survival according to the transplant era.

family history. The indication for LT was chronic liver failure in 42 patients (71.1%), including the fulminant form in 17 patients. Fifty patients received medical treatment (D-penicillamine, trientine, zinc sulfate, ammonium tetrathiomolybdate) prior to LDLT. The mean transplantation score was 17.7 ± 3.2. Retransplantation was indicated in a total of four patients due to chronic rejection in three cases and graft failure secondary to portal vein thrombosis in one case. Four patients showed tacrolimus-related seizure, which were successfully treated with cyclosporine conversion therapy. The one-, five-, 10-, and 15-yr patient and graft survival rates were 98.4%, 96.6%, 94.7% 77.5%, and 96.6%, 94.7%, 90.1%, 62.9%, respectively. There were six patient mortalities: *Pneumocystis* Pneumonia in one case, recurrent hepatitis C (a paternal graft with HCV-RNA +ve) in one case, de novo autoimmune hepatitis in one case, hypoxic ischemic encephalopathy in one case, and sepsis in two cases.

Fifty-one patients underwent LDLT for urea cycle deficiency (OTCD in 40 patients, CPS1D in nine patients, and ASS in two patients). The median age at LDLT was 3.8 ± 4.6 (0.2–16) yr. There were significant differences in age and body weight at LDLT between the patients with OTCD and patients with CPS1D (4.7 ± 7.8 and 0.8 ± 0.7 yr, 8.1 ± 2.9 vs. 4.7 ± 4.8 kg; $p < 0.001$), given that the patients with CPS1D exhibited a trend toward undergoing earlier LDLT than the patients with OTCD. The diagnosis was made according to a genetic analysis in 35 patients (68.6%). Seventeen patients (33.3%) demonstrated a relevant family history, including six patients with early death of a newborn(s) and 11 patients with a genetically proven heterozygote mother. Despite the administration of conventional medications with severe protein restriction, frequent hyperammonemia was observed in all patients. Four patients showed postoperative tacrolimus-related seizure. The mean transplantation score was 18.6 ± 3.0. The one-, five-, 10-, and 15-yr patient and graft survival rates were 96.1%, 96.1%, 96.1%, and 96.1%, respectively. Two patients died from hemophagocytic syndrome at three months and a traffic accident at four months after LDLT.

Twenty-nine patients received LDLT for organic acidemia (MMA in 20 patients and PA in nine patients) at a median age of 2.2 ± 2.8 (0.4–12) yr. Despite the administration of protein restriction (mean: 1.46 ± 0.81 g/kg/day) with medications (cobalamin, carnitine supplementation, and antibiotics to eradicate gut flora), recurrent metabolic decompensation was observed in all patients. The mean transplantation score was 18.6 ± 3.0. Two patients with PA had a family history of early death of a newborn. Four patients developed septic complications that resulted in mortality after LDLT. Post-transplant medications for the original liver disease were continued in all patients, with mild relief of protein restriction (mean; 1.72 ± 0.72 kcal/kg/day). Among the patients with MMA, four patients (20%) exhibited progressive renal insufficiency, and three patients (15%) demonstrated new onset of seizures following successful LDLT. None of the patients with PA developed cardiac insufficiency after LDLT. The one-, five-, and 10-yr patient and graft survival rates were 89.7%, 85.2%, and 85.2%, respectively.

LDLT for GSD was indicated in 15 patients, with a median age of 4.9 ± 4.3 (0.8–13) yr. The classification of GSD was type 1a in two patients, 1b in nine patients, and IV in four patients. The diagnosis was made based on a liver biopsy in five patients and a genetic analysis in 10 patients. The indication for LDLT was life-threatening hypoglycemia in 11 patients, chronic liver failure in three patients, and acute liver failure in two patients. There were six patient mortalities, five of which were due to septic complications after LDLT. Three of the five mortalities included patients with GSD type IV. The one-, five-, and 10-yr patient and graft survival rates were 80.0%, 66.7%, and 66.7%, respectively.

Nine patients received LDLT for PH1, with a mean age of 7.7 ± 6.2 (1–17) yr. Deficiency of alanine-glyoxylate aminotransferase of the liver was confirmed in all cases, and a genetic diagnosis was made in three cases. Three patients had a relevant family history. Five patients were on dialysis treatment at the time of LDLT, and four patients received sequential liver–kidney transplantation from a living donor(s). Three patients

Table 4. LDLT for each metabolic disorders

Diagnosis (n)	Wilson's disease (n = 59)	Urea cycle deficiency (n = 51)	Organic acidemia (n = 29)	Glycogen storage disease (n = 15)	Primary hyperoxaluria (n = 9)
Family history	4 (6.8%)	17 (33.3%)	2 (6.9%)	1 (6.6%)	3 (33.3%)
Donor age (yr)	41.7 ± 8.7 (22–68)	35.8 ± 6.8	33.6 ± 5.0	36.4 ± 9.2	39.9 ± 5.3
ABO incompatibility	5 (8.5%)	6 (11.8%)	5 (17.2%)	3 (20.0%)	1 (11.1%)
Age at onset (yr)	11.0 ± 4.4 (6–16)	1.1 ± 1.5 (0–2)	0.6 ± 1.7 (0–6)	0.1 ± 0.3 (0–1)	1.0 ± 0.8 (0.4–2)
Age at transplantation (yr)	11.4 ± 2.8 (6–17)	3.8 ± 4.6 (0.2–16)	2.2 ± 2.8 (0.4–12)	4.9 ± 4.3 (0.8–13)	7.7 ± 6.2 (1–17)
Indication of LTx	Chronic liver failure 42 Fulminant 17	Frequent hyperammonemia 51 Poor QOL 30	Metabolic decompensation 29 Poor QOL 29	Hypoglycemia 11 Chronic liver failure 3 Acute liver failure 2	Renal failure 9 Poor QOL 9
Transplantation score*	17.7 ± 3.2	19.3 ± 4.11	18.6 ± 3.0	14.0 ± 2.0	13.0 ± 2.0
Immunosuppression	Tac 86.0%, Tac+MMF 18.8% CyA 7.5%	Tac 72%, Tac+MMF20%, CyA 10%	Tac 86.2%, Tac+MMF3.4%, CyA 10.3%	Tac 80%, Tac+MMF 20%	Tac 77.8%, Tac+MMF 11.1%, CyA 11.1%
Acute and chronic rejection (%)	11.9, 3.4	9.8, 0	0, 0	6.6, 0	11.1, 0
Post LTx complication					
Hepatic artery thrombosis	1	0	0	0	1
Portal vein thrombosis	1	0	0	1	1
Biliary	1	1	0	0	0
Renal insufficiency	0	1	4	0	–
Seizure	4	4	3	3	0
Cause of death	*Pneumocystis* pneumonia Recurrent hepatitis C De novo autoimmune hepatitis Hypoxic–ischemic encephalopathy (epilepticus) Sepsis 2	Hemophagocytic syndrome Traffic accident	Sepsis 4	Sepsis 5 Liver failure after PV thrombus	Sepsis 3 Liver failure after HA/PV thrombus
Patient survival					
1 yr	98.4	96.1	89.7	80.0	55.6
5 yr	96.6	96.1	85.2	66.7	55.6
10 yr	94.7	96.1	85.2	66.7	55.6
15 yr	77.5	96.1	–	–	–

QOL, quality of life, LTx, liver transplantation, Tac, tacrolimus, MMF, mycophenolate mofetil, CyA, cyclosporine A, HA, hepatic artery, PV, portal vein.
*See Table 2.

died from septic complications. Mortality was observed in older patients (seven, nine, 15, and 17 yr), and three of five isolated liver transplant patients died. The one-, five-, and 10-yr patient and graft survival rates were 55.6%, 55.6%, and 55.6%, respectively.

Thirteen patients underwent LDLT for tyrosinemia at a median age of 8.1 ± 5.7 (1–21) months. Two patients had a family history of newborn death. LDLT was indicated for acute and chronic liver failure in all cases, with a median transplantation score of 19.1 ± 10.2. Three patient mortalities were noted, including sepsis in two cases and a traffic accident in one case.

Six patients received LDLT for citrullinemia at a median age of two and a half yr. All patients are currently doing well. Three other mortalities were observed, including a case of multi-organ failure in a patient with mitochondrial respiratory chain disorder, a case of sepsis in a patient with a bile acid synthetic defect and a case of sepsis secondary to biliary leakage in a patient with protoporphyria. Two of three patients with auxiliary orthotopic LDLT patients are doing well, one patient with OTCD received native hepatectomy due to the portal steal phenomenon.

Discussion

We reviewed the outcomes of 194 pediatric LDLT recipients with metabolic disorders. The one-, five-, 10-, and 15-yr patient and graft survival rates of the patients with metabolic disorders undergoing LDLT were 91.2%, 87.9%, 87.0%, and 79.3%, and 91.2%, 87.9%, 86.1%, and 74.4%, respectively. The present results compare favorably with recently published data from an outstanding series regarding deceased LT (16–18). Patient survival was significantly better for patients undergoing LDLT more recently, with a five-yr survival rate of 89.9%. The recent achievement of better patient survival might be due to perioperative nutritional, immunological, and surgical management. Non-Wilson, non-urea cycle patients appear to be more associated with medical complications in their mortality causes. These patients necessitate lifelong strict medication and protein restriction even after successful LDLT, and this might be associated with worse patient survival.

Due to the unavailability of deceased donors, LDLT has been employed as a major organ resource for LT in our country. In the present study, 95.6% of the donors were parents, and an obligate heterozygous carrier of the recipient's disorder may be used as a live donor. There have been limited numbers of LDLT series using heterozygous donors in the literature, and the long-term risks of heterozygous carrier donors have not been fully documented (19, 20). Most cases of inherited metabolic disorders are autosomal recessive, and transplantation from carrier parents with autosomal recessive diseases (50% enzyme activity) has demonstrated successful LDLT results (21). It has been reported that the use of genetically proven heterozygous donors in patients with autosomal recessive disease shows no negative impact on either the donors or recipients (6, 7, 9–11, 19). With regard to X-linked OTCD, it has been reported that heterozygote females are at risk of the disease, presumably due to liver mosaicism (22). In the present study, 19 of the 48 patients with OTCD (39.6%) received maternal grafts, given the potential for heterozygote carriers, and no morbidities or mortalities related to the use of heterozygous carriers were observed. Recently, Wakiya et al. (7) reported that the liver tissue in asymptomatic maternal carriers should be extracted via liver biopsies for enzymatic analyses prior to LDLT. Inui et al. (23) demonstrated that the OTC activity is different in each segment of the liver in OTCD recipients, ranging from 9.7% in segment VI to 34.2% in segment II. Moreover, intrahepatic variation of enzyme activity was reported in a study of affected carriers (24). With respect to these studies, it is obvious that symptomatic carriers should not be as potential donor candidates for LDLT to avoid potential hyperammonemic event. A portion of the liver tissue should be used to investigate the correlation between genetic errors and the enzyme activity, while the remainder must be preserved for future analyses to precisely evaluate the impact of the use of heterozygous carriers of disorders on the risk and safety of the procedure in both donors and recipients.

The present study clearly demonstrated a significant increase in the number of LDLT procedures for inborn errors of metabolism and changes in the indications for LDLT over the past two decades. Although there are differences between the JLTS series and other outstanding series of patients with original liver disease (16–18), the proportion of recipients with Wilson's disease decreased from 43.9 to 12.7% over the most recent 10 yr in the present series. The development of conventional medical treatment with copper chelate (D-penicillamine, trientine hydrochloride) and zinc salt combined with early diagnosis means that the number of patients who can be maintained with medications without undergoing LT is expected to increase in Japan (25). Patients with Wilson's disease should

undergo a trial of treatment with medications together with considering LDLT.

On the other hand, the number of cases of urea cycle disorder is increasing from 15.5 to 30.9% over the most recent 10 yr. Even after successful treatment of severe hyperammonemia with pharmaceutical therapy with/without hemodiafiltration, most patients require a considerable treatment regimen and may have handicaps, such as impaired development, due to recurrent episodes of hyperammonemia (26). It has been reported that patients with neonatal onset of urea cycle disorders exhibit remarkable gains in their development after undergoing successful LT (1). Given the risk of continued neurological compromise, the potential to improve development represents a major benefit of early LDLT. In the present JLTS study, although there were no significant differences, the proportion of transplanted recipients with urea cycle disorders less than six months of age increased from 0% to 30.8% over the past two decades.

The use of LDLT for organic acidemia has also increased in recent years. Although implanted liver grafts produce deficient enzymes in patients with organic acidemia, the procedure only partially corrects the biochemical defects, as the enzymes are expressed in most cells and surgery may not prevent the development of progressive renal and neurological deterioration (27). However, the use of LDLT for organic acidemia showed acceptable patient and graft survival, with a rate of 85.2% at 10 yr, in the present study. Charkrapani et al. (27) reported that the benefits of an improved quality of life associated with the elimination of episodes of decompensation and improved protein tolerance must be weighed against the potential for renal and neurological injury. We agree with these results that LDLT does not cure the disease, although it may decrease the disease severity.

LDLT for GSD has recently been indicated by the JLTS. As a result of early diagnosis and radical treatment with nocturnal nasogastric feeding and uncooked cornstarch, the prognosis of GSD has improved dramatically. After starting radical dietary treatment, however, the development of neurological impairment as a consequence of metabolic derangement has been reported in 40% of patients with GSD (28). LT can be recommended from this point of view because the procedure can reduce the magnitude of progressive neurological disability caused by poor metabolic control. The patient and graft survival of patients with GSD are not sufficient due to septic complications. Proper infectious management (including neutropenia management in patients with GSD 1b) and the administration of regimens of immunosuppression are necessary in this population.

PH1 is a very rare inherited metabolic disorder characterized by a deficiency of the liver-specific enzyme alanine, alanine-glyoxylate aminotransferase, resulting in the overproduction and excessive urinary excretion of oxalate with end-stage renal disease. Although the number of cases was limited, four of the nine patients in this study who received sequential liver–kidney transplantation from a living donor are doing well. Mortality was observed in the patients transplanted much too late. It has been reported that combined liver–kidney transplantation is the best treatment for patients with PH1 with end-stage renal disease (29). In our country, small deceased donors are less likely to become available, and living donor liver–kidney transplantation is often the only treatment modality for patients with pediatric liver–kidney disease (12). Due to the unequivocal risks of the potential live donor candidate, especially liver–kidney donors, efforts should be made for early LT and to increase the number of deceased donors in order to minimize the need for living donors.

There is no clear score system for indications for LT in patients with inherited metabolic disorders. We retrospectively analyzed a grading score system (Table 2) and found that the system is an effective indicator for LT for patients with metabolic disorders. The mean transplant score was 16.3 ± 8.2 (3-37), while five patients (2.5%; Wilson's disease in two cases, familial hypercholesterolemia in two cases, and tyrosinemia in one case) demonstrated transplantation scores of <10. Although this study was a retrospective analysis, the transplantation score is useful for considering the indications and timing of LT because it reflects the effectiveness of conventional medical treatment, the quality of life, and the mental/physical status.

In conclusion, the present study confirmed that LDLT performed to treat inherited metabolic disorders can provide an acceptable survival rate over 15 yr, although most donors in the present series were heterozygous for their respective recipient's disorder. As neither mortality nor morbidity related to heterozygosis was observed, an intensive investigation should be conducted in this donor population. Improving understanding of the long-term suitability of this treatment modality will require the registration and ongoing evaluation of all patients with inherited metabolic disease considered for LT.

Acknowledgments

This work was supported in part by grants from the Scientific Research Fund of the Ministry of Education and a Research Grant for Immunology, Allergy and Organ Transplant, Rare and Intractable Disease from the Ministry of Health, Labor and Welfare, Japan (H24-08, H24-014, H25-06), and the Foundation for Growth Science, Japan.

Conflicts of interest

No conflicts of interest.

Appendix

The following constitute the pediatric JLTS research group enrolled in this study:

Shinji Uemoto (Kyoto University, Kyoto), Norihiro Kokudo (Tokyo University, Tokyo), Susumu Satomi (Tohoku University, Miyagi), Yukihiro Inomata (Kumaoto University, Kumamoto), Tastuo Kuroda (Keio University, Tokyo), Masahiro Fukuzawa (Osaka University, Osaka), Koichi Mizuta (Jichi University, Tochigi), Yasutsugu Takada (Ehime University, Ehime), Miyuki Kouno (Kanazawa Medical University, Kanazawa), Tatsuya Suzuki (Fujita Health University, Nagoya), Takahito Yagi (Okayama University, Okayama), Norio Yoshimura (Kyoto Prefectural University of Medicine, Kyoto), Tomoaki Taguchi (Kyushu University, Fukuoka), Hiroyuki Kuwano (Gunma University, Gunma), Izumi Takeyoshi (Gunma University, Gunma), Kenichi Hakamada (Hirosaki University, Hirosaki), Hiroto Egawa (Tokyo Women's Medical University, Tokyo), Shinichi Miyagawa (Shinshu University, Nagano), Katsuyoshi Hatakeyama (Niigata University, Niigata), Masato Shinkai (Kanagawa Children's Medical Center, Kanagawa), Tetsuo Ota (Kanazawa University, Kanazawa), Syuji Isa (Mie University, Mie), Masaru Miyazaki (Chiba University, Chiba), Keiichi Kubota (Dokkyo Medical University, Tochigi), Mitsukazu Goto (Fukushima Medical University, Fukushima), Akinobu Taketomi (Hokkaido University, Hokkaido), Masahiko Watanabe (Kitasato University, Kanagawa), Hiromitsu Takeyama (Nagoya City University), Yasuhiro Ogura (Nagoya University, Nagoya), Seisuke Sakamoto, Mureo Kasahara (National Center for Child Health and Development, Tokyo).

References

1. Stevenson T, Millan MT, Wayman K, et al. Long-term outcome following pediatric liver transplantation for metabolic disorders. Pediatr Transplant 2010; 14: 268–275.
2. Treem WR. Liver transplantation for non-hepatotoxic inborn errors of metabolism. Curr Gastroenterol Rep 2006; 8: 215–223.
3. Lee V, Fecteau A, Shepherd R, et al. Outcomes of 5-year survivors of pediatric liver transplantation: Report on 461 children from a North American multicenter registry. Pediatrics 2008; 122: 1128–1135.
4. Morioka D, Kasahara M, Takada Y, et al. Living donor liver transplantation for pediatric patients with inheritable metabolic disorders. Am J Transplant 2005; 5: 2754–2763.
5. Cheng F, Li GQ, Zhang F, et al. Outcomes of living-related liver transplantation for Wilson's disease: A single-center experience in China. Transplantation 2009; 87: 751–757.
6. Yoshitoshi EY, Takada Y, Oike F, et al. Long-term outcomes for 32 cases of Wilson's disease after living-donor liver transplantation. Transplantation 2009; 87: 261–267.
7. Wakiya T, Sanada Y, Mizuta K, et al. Living donor liver transplantation for ornithine transcarbamylase deficiency. Pediatr Transplant 2011; 15: 390–395.
8. Kasahara M, Sakamoto S, Shigeta T, et al. Living-donor liver transplantation for carbamoyl phosphate synthetase 1 deficiency. Pediatr Transplant 2010; 14: 1036–1040.
9. Kasahara M, Sakamoto S, Kanazawa H, et al. Living-donor liver transplantation for propionic academia. Pediatr Transplant 2012; 16: 230–234.
10. Morioka D, Kasahara M, Horikawa R, Yokoyama S, Fukuda A, Nakagawa A. Efficiency of living donor liver transplantation for patients with methylmalonic academia. Am J Transplant 2007; 7: 2782–2787.
11. Kasahara M, Horikawa R, Sakamoto S, et al. Living donor liver transplantation for glycogen storage disease type 1b. Liver Transpl 2009; 15: 1867–1871.
12. Nakamura M, Fuchinoue S, Nakajima K, et al. Three cases of sequential liver-kidney transplantation from living-related donors. Nephrol Dial Transplant 2001; 16: 166–168.
13. Iwama I, Baba Y, Kagimoto S, et al. Case report of a successful liver transplantation for acute liver failure due to mitochondrial respiratory chain complex III. Transplant Proc 2011; 43: 4025–4028.
14. Kasahara M, Umeshita K, Inomata Y, Uemoto S. Long-term outcomes of pediatric living donor liver transplantation in japan: An analysis of more than 2,200 cases listed in the registry of the Japanese liver transplantation society. Am J Transplant 2013; 13: 1830–1839.
15. Kasahara M. Living donor liver transplantation for metabolic liver disease. J Pediatr Practice 2013; 76: 110–116.
16. Arnon R, Kerkar N, Davis MK, et al. Liver transplantation in children with metabolic disease: The studies of pediatric liver transplantation experience. Pediatr Transplant 2010; 14: 796–805.
17. Sze YK, Taylor RM, Bansal S, et al. Pediatric liver transplantation for metabolic liver disease; experience at King's college hospital. Transplantation 2009; 87: 87–93.
18. Kaylar LK, Rasmussen CS, Dykstra DM, et al. Liver transplantation in children with metabolic disorders in the United States. Am J Transplant 2003; 3: 334–339.
19. Morioka D, Takada Y, Kasahara M, et al. Living donor liver transplantation for noncirrhotic inheritable metabolic liver diseases: Impact of the use of heterozygous donors. Transplantation 2005; 80: 623–628.
20. Braegger C, Florman S, Shneider B. Living-related liver transplantation in inherited metabolic liver disease: Feasibility and cautions. J Pediatr Gastroenterol Nutr 2001; 33: 520–521.
21. Wong DA. Ornithine transcarbamylase deficiency: Are carrier females suitable donors? Pediatr Transplant 2012; 16: 535–537.
22. Yorifuji T, Muroi J, Uematsu A, et al. X-inactivation pattern in the liver of manifesting female with ornithine transcarbamylase (OTC) deficiency. Clin Genet 1998; 54: 349–353.

23. Inui A, Fujisawa T, Mogi A, et al. Living related liver transplantation for a ornithine transcarbamylase deficiency. Jap J Pediatr 1997; 101: 963–967.
24. Tuchman M. The clinical, biochemical, and molecular spectrum of ornithine transcarbamylase deficiency. J Lab Clin Med 1992; 120: 836–850.
25. Oya Y, Okajima H, Honda M, et al. Re-evaluation of the indications for liver transplantation in Wilson's disease based on the outcomes of patients referred to a transplant center. Pediatr Transplant 2013; 17: 369–373.
26. Maestri NE, Hauser ER, Bartholomew D, Brusilow SW. Prospective treatment of urea cycle disorders. J Pediatr 1991; 119: 923–928.
27. Chakrapani A, Sivakumar P, McKiernan PJ, Leonard JV. Metabolic stroke in methylmalonic acidemia five years after liver transplantation. J Pediatr 2002; 140: 261–263.
28. Rake JP, Visser G, Labrune P, Leonard JV, Ullrich K, Smit GPA. Glycogen storage disease type 1: Diagnosis, management, clinical course and outcome. Results of the European Study on Glycogen Storage Disease Type 1 (ESGSD1). Eur J Pediatr 2002; 161: S20–S30.
29. Ellis SR, Hulton SA, McKiernan PJ, De Goyet JVD, Kelly DA. Combined liver-kidney transplantation for primary hyperoxaluria type 1 in young children. Nephrol Dial Transplant 2001; 16: 348–354.

ORIGINAL ARTICLE

Nationwide Survey of the Outcomes of Living Donor Liver Transplantation for Hepatoblastoma in Japan

Seisuke Sakamoto,[1] Mureo Kasahara,[1] Koichi Mizuta,[2] Tatsuo Kuroda,[3] Takahito Yagi,[4] Tomoaki Taguchi,[5] Yukihiro Inomata,[6] Koji Umeshita,[7] and Shinji Uemoto,[8] for the Japanese Liver Transplantation Society

[1]Transplantation Center, National Center for Child Health and Development, Tokyo, Japan; [2]Department of Transplant Surgery, Jichi Medical University, Tochigi, Japan; [3]Department of Pediatric Surgery, Keio University, Tokyo, Japan; [4]Department of Surgery, Okayama University, Okayama, Japan; [5]Department of Pediatric Surgery, Kyushu University, Fukuoka, Japan; [6]Department of Transplant Surgery, Kumamoto University, Kumamoto, Japan; [7]Department of Surgery, Osaka University, Osaka, Japan; and [8]Department of Surgery, Kyoto University, Kyoto, Japan

Recently, liver transplantation (LT) has been increasingly performed for unresectable hepatoblastoma (HB) with acceptable results. We conducted a national survey of cases undergoing living donor liver transplantation (LDLT) for HB to evaluate their outcomes. Thirty-nine patients (28 males and 11 females with a median age at LDLT of 3.6 years) who had undergone LDLT for HB by the end of 2009 were enrolled in this study. The clinical data were collected from their medical records via a questionnaire survey in 2011 (median follow-up = 4.6 years). Thirteen patients (33.3%) had extrahepatic lesions before LDLT. Thirty-eight patients (97.4%) received chemotherapy, and 15 (38.5%) underwent hepatectomy before LDLT. Twenty-seven patients (69.2%) were alive without recurrence after LDLT, and 12 patients (30.8%) suffered from recurrence. The most common site of recurrence was the lung (9 cases), which was followed by the graft liver (6 cases). The median interval from LDLT to recurrence was 5.5 months. Four of the 9 cases (44.4%) with lung metastasis underwent surgical resection, and 3 were alive without any tumor recurrence. Eight patients died because of tumor recurrence. The multivariate landmark analysis revealed that the independent recurrence risk factors were a high alpha-fetoprotein (AFP) level at diagnosis [≥500,000 ng/mL; hazard ratio (HR) = 7.86, $P = 0.010$], the presence of extrahepatic lesions before LDLT (HR = 3.82, $P = 0.042$), and a high AFP level at LDLT (≥4000 ng/mL; HR = 9.19, $P = 0.036$). The actuarial 3- and 5-year patient survival rates were 84.3% and 77.3%, respectively. In conclusion, with appropriate timing for scheduled LT, LDLT provides a valuable alternative treatment with excellent results for children with HB. *Liver Transpl 20:333-346, 2014.* © 2013 AASLD.

Received July 18, 2013; accepted November 18, 2013.

Abbreviations: ACR, acute cellular rejection; AFP, alpha-fetoprotein; auto-SCT, autologous hematopoietic stem cell transplantation; CBDCA, carboplatin; CI, confidence interval; C-index, concordance index; CITA, cisplatin and tetrahydropyranyl-doxorubicin; CNI, calcineurin inhibitor; CPA, cyclophosphamide; CPT-11, irinotecan; HB, hepatoblastoma; HI-MEC, ifosfamide, etoposide, carboplatin, and melphalan; HIMT, ifosfamide, etoposide, melphalan, and thiotepa; HR, hazard ratio; HV, hepatic vein; ITEC, ifosfamide, carboplatin, tetrahydropyranyl-doxorubicin, and etoposide; IVC, inferior vena cava; JPLT, Japanese Study Group for Pediatric Liver Tumor; LDLT, living donor liver transplantation; LL, left lobe; LLS, left lateral segment; LT, liver transplantation; N/A, not assessed; PD, peritoneal dissemination; POST-TEXT, Posttreatment Extent of Disease; PRETEXT, Pretreatment Extent of Disease; PV, portal vein; PVTT, portal vein tumor thrombus; ROC, receiver operating characteristic; SIOPEL, Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology; THP-ADR, tetrahydropyranyl-doxorubicin; VP-16, etoposide.

There are no conflicts of interest to disclose.

This work was supported in part by grants from the Scientific Research Fund of the Japanese Ministry of Education and by a research grant for immunology, allergy, and organ transplantation from the Japanese Ministry of Health, Labor, and Welfare and the Foundation for Growth Science.

Address reprint requests to Seisuke Sakamoto, M.D., Ph.D., Transplantation Center, National Center for Child Health and Development, 2-10-1 Okura, Setagaya, Tokyo 157-8535, Japan. Telephone: +81-3-3416-0181; FAX: +81-3-3416-2222; E-mail: sakamoto-si@ncchd.go.jp

DOI 10.1002/lt.23803
View this article online at wileyonlinelibrary.com.
LIVER TRANSPLANTATION.DOI 10.1002/lt. *Published on behalf of the American Association for the Study of Liver Diseases*

Hepatoblastoma (HB) is the most frequent liver tumor of childhood, and it accounted for approximately 1% of pediatric malignant tumors in a previous report.[1] According to a recent report, the incidence of this tumor has increased over time, and HB is almost exclusively seen in children < 5 years old.[2] Despite treatment with chemotherapy and surgical resection, the prognosis of cases with advanced disease, which is defined as a huge tumor or multifocal tumors occupying the entire liver (precluding complete resection) and/or distant metastatic disease, is poor.[3] Although preoperative chemotherapy makes more than 60% of initially unresectable tumors resectable, 20% of these tumors remain unresectable.[4] Liver transplantation (LT) has been indicated for those cases as the only therapeutic option, and previous studies have shown an improvement in the survival rate of 50% to 90% 5 years after LT.[5,6]

Living donor liver transplantation (LDLT) has been established as the primary therapeutic modality for end-stage liver disease in children, especially in Asian countries.[7] A previous study from a Kyoto group showed that LDLT might allow for the optimal timing of LT in cases with unresectable HB because there is no delay between the completion of chemotherapy and the scheduled LT.[8]

We herein report the results of a nationwide survey of outcomes of LDLT for HB in Japan.

PATIENTS AND METHODS

The primary data related to the cases undergoing LDLT for HB in Japan were collected from the registry kept by the Japanese Liver Transplantation Society. Based on the results of the primary data, a more detailed survey was mailed to the 14 institutions that performed LDLT for HB patients. Forty-one patients underwent LDLT between February 1996 and December 2009. Thirty-nine patients were finally enrolled in the current study because 1 patient died of graft failure on postoperative day 5 and another patient underwent LDLT for liver failure after multiple sessions of transarterial chemoembolization and right lobectomy. There was no tumor recurrence at the time of LDLT, and the patient did not exhibit tumor recurrence during the follow-up period after LDLT. The cases were followed until June 2011 with a median follow-up period of 4.6 years (range = 6 months to 15.2 years). The relevant clinical courses, biochemical and hematological data, pathological findings, and radiological images were collected to construct a database, and then they were analyzed by statistical analysis with permission from the institutional review board of the National Center for Child Health and Development and the Japanese Liver Transplantation Society.

Pretransplant Management for HB

The Pretreatment Extent of Disease (PRETEXT) staging system was used for the pretreatment staging of tumors, and the Posttreatment Extent of Disease (POST-TEXT) staging system was used for the post-chemotherapy staging of tumors before any surgical resection on the basis of radiological findings. The pretransplant treatment, such as chemotherapy and surgical resection, was selected by each institution, although the Japanese Study Group for Pediatric Liver Tumor (JPLT) has proposed a nationwide protocol for liver tumors in childhood, and this served as a background guideline.

The current protocol, JPLT-2, has been described elsewhere[9]; in brief, PRETEXT I tumors were primarily resected, and PRETEXT II-IV cases were treated with preoperative chemotherapy. At least 2 courses of a combination of cisplatin and tetrahydropyranyl-doxorubicin (THP-ADR), which was designated CITA, were repeated preoperatively. When CITA failed to induce a partial response, a combination of ifosfamide, carboplatin (CBDCA), THP-ADR, and etoposide (VP-16), which was designated ITEC, was given until the tumor became resectable. Postoperative chemotherapy was used in all cases. PRETEXT III, PRETEXT IV, and metastatic cases were treated with 2 courses of CITA. Patients who required salvage with ITEC preoperatively were treated with 2 courses of ITEC. If a complete response was not obtained at this point, 2 additional courses were added. Metastatic cases were treated with high-dose chemotherapy, which consisted of a combination of ifosfamide, VP-16, CBDCA, and melphalan (designated the Hi-MEC protocol) or a combination of ifosfamide, VP-16, melphalan, and thiotepa (designated the Hi-MT protocol), as proposed by the JPLT group,[10,11] and with autologous hematopoietic stem cell transplantation (auto-SCT), although the metastatic lesions that were considered to be resectable were surgically resected at the discretion of each institution.

LDLT

The indications for and timing of LDLT were left to the discretion of each institution. In each case, after the family's consent to proceed with the operation was obtained, a thorough medical evaluation was performed to determine the suitability of the donor. Donors were selected on the basis of the results of a medical evaluation, including liver function tests, ABO blood group typing, and graft/recipient size matching. The graft type was selected according to the graft/recipient weight ratio or the graft volume/standard liver volume ratio.[7,8,12,13] All of the donors were the children's parents, except for 1 grandfather. The ages of the donors ranged from 23 to 64 years with a median age of 34 years. The blood type combination was incompatible in 2 cases. The graft type was a left lobe (LL) in 6 cases, a left lateral segment (LLS) in 31 cases, and a reduced LLS in 2 cases. The native inferior vena cava (IVC) was completely removed in 4 cases during whole hepatectomy. Thereafter, 1 patient underwent the reconstruction of a new IVC with the vessel graft from his donor's internal

jugular vein (case 29). The other 3 patients did not undergo IVC reconstruction (cases 13, 16, and 18) because they all demonstrated sufficient venous return via collaterals to the azygous systems, which was possibly established by longstanding tumor compression on the IVC; this situation was radiologically confirmed before LDLT, and all patients were verified to be hemodynamically stable by test clamping of the IVC during LDLT. The native IVC wall was partially removed in 2 cases (eg, the anterior wall; cases 34 and 36). Having previously undergone liver resection, 1 patient (case 8) showed an absence of the IVC. The manner of biliary reconstruction was hepaticojejunostomy in 23 cases and duct-to-duct anastomosis in 16 cases. The initial immunosuppression protocol was tacrolimus in all cases except for 1 case in which cyclosporine was administered. Although a target trough level of the calcineurin inhibitor (CNI) was selected at the discretion of each institution on the basis of each patient's condition (eg, renal function), target trough levels of 8 to 10 mg/L for the first 2 weeks, 6 to 8 mg/L for days 15 to 28 after LDLT, and 4 to 6 mg/L from day 29 onward and during posttransplant chemotherapy were maintained in the majority of the cases using tacrolimus. Low-dose steroid therapy, which was basically tapered off by 3 months after LDLT, was used in 25 cases as maintenance immunosuppression, although the corticosteroid was given only intraoperatively at the time of graft reperfusion in 14 cases. The immunosuppression regimen was performed for the 2 cases with a blood type–incompatible combination (cases 18 and 37) in the same manner as that for the cases with a blood type–compatible combination because of the younger age at the time of LDLT.[14] The pathological diagnoses, such as acute cellular rejection (ACR) and chronic rejection, were made according to the Banff criteria.[15] When ACR was confirmed, patients were treated with a high-dose corticosteroid.

Posttransplant Management for HB

The postoperative chemotherapy regimen was selected at the discretion of each institution. If the patient had shown a sufficient response and no dose-dependent side effects of preoperative chemotherapy, the same chemotherapy regimen was adopted postoperatively. If not, then irinotecan (CPT-11) was advocated for use as postoperative chemotherapy.

Statistical Analysis

The tumor recurrence–free survival curves were calculated with the Kaplan-Meier method. The log-rank test was used to evaluate the effects of different characteristics on tumor recurrence. A receiver operating characteristic (ROC) analysis was used to evaluate the ability of the serum alpha-fetoprotein (AFP) level to predict tumor recurrence after LDLT and to choose the optimal cutoff value for the subsequent analysis. To select the optimal cutoff values, the concordance index (C-index) was calculated for each cutoff point on the ROC curve.[16,17] The C-index for a cutoff point was defined as the area of the quadrilateral with vertices on the cutoff point on the ROC curve and points (0, 0), (1, 0), and (1, 1) on the ROC graph. The value estimated the probability that the predictors and the outcomes were concordant. The C-index was calculated with the following formula:

$$\text{C-index} = (\text{Sensitivity} + \text{Specificity})/2$$

We defined the optimal cutoff value as the point showing the highest C-index among the values with a specificity > 0.70. The selected cutoff values were 500,000 ng/mL for AFP at diagnosis (with C-index, sensitivity, and specificity values of 0.78, 0.83, and 0.74, respectively) and 4000 ng/mL for AFP at LDLT (with values of 0.82, 0.92, and 0.74, respectively; Fig. 1). A multivariate Cox regression analysis with backward elimination was used to evaluate the association between tumor recurrence and pretransplant patient characteristics and to estimate the hazard ratio (HR) and its 95% confidence interval (CI). A P value of 0.05 was used for variable selection and was regarded as significant. The IBM SPSS statistics software program (version 19.0, IBM SPSS, Inc., Chicago, IL) was used for the statistical analysis.

RESULTS

The cases included 28 males and 11 females with a median age at the time of diagnosis of 2.5 years, and the ages ranged from 0.2 to 16.6 years. The details of the patient characteristics are summarized in Table 1 (before LDLT) and Table 2 (after LDLT).

Patient Characteristics Before LDLT

The PRETEXT staging was IV in 22 cases (56.4%) and III in 15 cases (38.5%). There was 1 case with PRETEXT stage I (2.6%), and there was 1 case with PRETEXT stage II (2.6%). The median serum AFP level at diagnosis was 375,480 ng/mL, and it ranged from 1835 to 4,400,000 ng/mL. All of the cases, except for 1 case with biliary atresia (case 5) for whom HB was incidentally found during the pathological examination of the explanted native liver, received pretransplant chemotherapy. Each child received 2 to 17 cycles of chemotherapy (median = 6 cycles) before LDLT. The majority of the cases followed the chemotherapy protocol proposed by the JPLT group. A pretransplant chemotherapy protocol containing CITA was the initial protocol for 36 of the 38 cases (94.7%). Twenty of the 28 patients who showed a poor response to chemotherapy with CITA followed an additional protocol using ITEC. Ten patients (26.3%) underwent transarterial chemotherapy with or without embolization before LDLT. Nine patients (23.7%) underwent auto-SCT with high-dose chemotherapy; the Hi-MEC protocol was used in 5 cases, and the Hi-MT protocol was used in 5 cases [this included a case undergoing auto-SCT twice with both high-dose chemotherapy protocols (case 24)]. The indication for

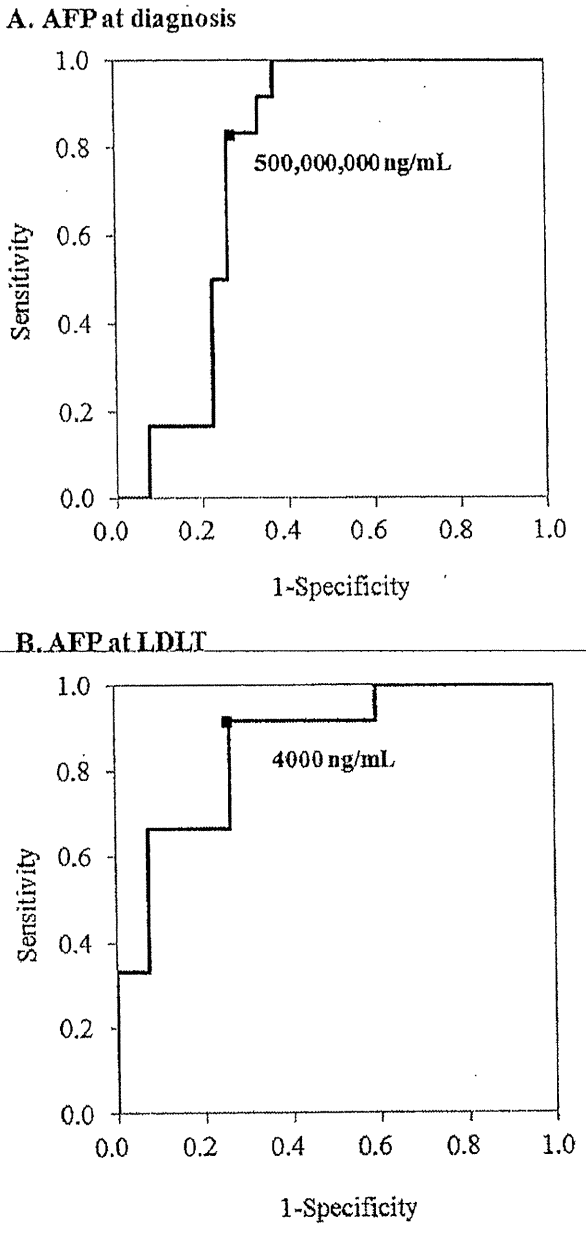

Figure 1. ROC curves for predicting tumor recurrence after LDLT: (A) AFP at diagnosis and (B) AFP at LDLT.

auto-SCT was an unresectable tumor refractory to multiple sessions of conventional-dose chemotherapy after liver resection in 6 cases (cases 6, 9, 13, 14, 24, and 34) and without liver resection in 3 cases (cases 17, 18, and 29). The POST-TEXT staging was IV for 22 cases (62.9%), III for 11 patients (31.4%), and I for 2 patients (5.7%).

Before LDLT, liver resection was performed in 15 cases (38.5%), which included 12 cases after chemotherapy and 3 cases before chemotherapy. Seven of these 15 patients (46.7%) underwent liver resection 2 or 3 times. The types of liver resections included right trisectionectomy (n = 6), right lobectomy (n = 2), left trisectionectomy (n = 3), left hepatectomy (n = 2), right anterior sectionectomy (n = 1), right posterior sectionectomy (n = 1), left lateral segmentectomy (n = 1), and nonanatomical tumor resection (n = 8).

Thirteen patients (33.3%) had extrahepatic lesions before LDLT. One showed direct tumor invasion into the IVC, which was completely resected along with total hepatectomy, at the time of LDLT. Three cases showed tumor invasion into the portal veins (PVs). The tumor thrombus radiologically disappeared after systemic chemotherapy in 1 of the 3 cases (case 33), although the tumor thrombi remained in the other cases at the time of LDLT and were completely removed together with the native portal venous trunk. Two patients showed tumor invasion into other adjacent organs, the stomach and transverse colon, which were completely resected by bowel resection with safe tumor margins. Two patients had a metastatic lesion in the abdominal cavity, which was completely resected 1 and 2 years before LDLT. Two patients had an episode of tumor rupture at the time of onset, and 1 of these patients required urgent hemostasis by transarterial embolization (case 34), although both were confirmed to be free from malignant cells by peritoneal wash cytology at the time of LDLT. Three patients showed lung metastases. One of them underwent partial resection for 4 lesions of lung metastases 3 months before LDLT (case 29), and the metastatic lesions radiologically disappeared after systemic chemotherapy in the other 2 cases.

Patient Characteristics at LDLT

LDLT was primarily indicated because of the presence of an unresectable tumor after systemic chemotherapy (23 cases or 59.0%). The indication for LDLT was unresectable tumor recurrence after hepatectomy, which was once performed for a resectable tumor after systemic chemotherapy, in 15 cases (38.5%). The median age at the time of LDLT was 3.6 years (range = 0.8 to 22.1 years). The mean interval between the diagnosis and LDLT was 1.5 ± 1.8 years (range = 0 days to 6.8 years). The median serum AFP level at LDLT was 3155 ng/mL (range = 10-1,175,690 ng/mL). Seventeen cases (43.6%) showed a less than 2-log decline in the serum AFP level during the period from diagnosis to LDLT, and 2 cases did not show any decline; 1 of the latter 2 cases had an increase in the serum AFP level at LDLT.

Overall Outcomes After LDLT

Thirteen patients (33.3%) experienced more than 1 episode of ACR and were successfully treated with steroid pulse therapy. Eighteen patients (46.2%) developed surgical complications, which included 10 biliary complications (biliary strictures in 8 cases and biliary leakage in 2 cases), 4 cases of intra-abdominal bleeding, and 1 case each of bowel perforation, bowel

TABLE 1. Patient Characteristics Before LDLT

Case Number	Age at Diagnosis (Years)	Sex	PRETEXT Stage	AFP at Diagnosis (ng/mL)	Extrahepatic Lesion(s) (Site)	Chemotherapy Protocol	Cycles of Chemotherapy (n)	POST-TEXT Stage	Liver Resections (n)	Auto-SCT
1	9.7	Male	IV	5942	No	Others*	6	IV	Yes (1)	No
2	0.2	Male	III	677,400	No	CITA/others	6	III	No	No
3	3.7	Male	II	529,000	No	CITA/others	8	N/A†	Yes (1)	No
4	1.8	Male	IV	590,000	Yes (stomach)	CITA*	10	IV	No	No
5	4.6	Female	III	12,900	No	None	N/A	N/A	No	No
6	9.0	Male	IV	2600	No	CITA/others*	7	IV	Yes (1)	Yes
7	2.6	Female	IV	1,500,000	No	CITA*	2	IV	No	No
8	0.4	Male	III	15,000	No	CITA/others	17	N/A†	Yes (1)	No
9	3.6	Male	IV	2,700,000	No	CITA/ITEC	5	III	Yes (3)	Yes
10	3.9	Male	IV	266,000	No	CITA	2	IV	No	No
11	3.2	Male	IV	375,480	Yes (colon)	CITA/ITEC*	16	III	Yes (1)	No
12	11.4	Male	III	36,200	No	CITA	5	III	Yes (1)	No
13	2.5	Female	IV	887,800	Yes (IVC)	CITA/others*	5	IV	Yes (2)	Yes
14	4.0	Male	III	3600	No	Others	8	III	Yes (2)	Yes
15	0.6	Female	III	1,000,000	No	CITA/ITEC	4	IV	No	No
16	0.8	Male	III	4,400,000	No	CITA/ITEC	6	III	No	No
17	4.3	Male	III	1,880,000	No	CITA/ITEC/ others	8	IV	No	Yes
18	1.5	Male	IV	186,699	No	CITA/others	7	III	No	Yes
19	1.1	Female	III	249,400	No	CITA/ITEC	9	IV	No	No
20	11.4	Female	IV	455,700	No	CITA/ITEC/ others	8	III	Yes (1)	No
21	0.5	Female	III	243,800	No	CITA	3	IV	No	No
22	7.9	Male	IV	3000	Yes (omentum)	CITA/others*	15	III	Yes (2)	No
23	3.2	Male	IV	255,840	Yes (PVTT)	CITA/ITEC	4	IV	No	No
24	1.5	Male	III	1,202,849	No	CITA/ITEC/ others	13	III	Yes (2)	Yes‡
25	0.8	Female	IV	2,237,000	No	CITA/ITEC	4	IV	No	No
26	2.2	Male	III	1835	No	CITA	2	III	No	No
27	1.1	Male	III	836,600	No	CITA/ITEC	4	IV	No	No
28	6.9	Male	IV	866,000	Yes (rupture)	CITA/ITEC*	2	IV	No	No
29	1.8	Male	IV	699,700	Yes (lung)	CITA/ITEC	5	IV	No	Yes
30	3.6	Female	IV	723,172	Yes (PVTT)	CITA/ITEC	4	IV	No	No
31	1.1	Female	IV	1,651,000	Yes (lung)	CITA/ITEC	8	IV	No	No
32	1.9	Male	IV	590,000	Yes (lung)	CITA/ITEC	6	IV	No	No
33	2.7	Male	IV	470,500	Yes (PVTT)	CITA	3	IV	No	No
34	16.6	Male	III	5187.6	Yes (rupture)	CITA/ITEC/ others	11	N/A†	Yes (3)	Yes
35	3.8	Male	I	83,470	Yes (lymph node)	CITA/others*	10	I	Yes (2)	No
36	1.4	Female	III	1884	No	CITA	2	I	Yes (1)	No
37	1.4	Male	IV	121,900	No	CITA/ITEC*	8	IV	No	No
38	0.9	Male	IV	51,000	No	CITA/ITEC	7	IV	No	No
39	0.8	Male	IV	65,000	No	CITA/ITEC	4	IV	No	No

*The case underwent transarterial chemotherapy with or without embolization.
†The case underwent liver resection before chemotherapy.
‡The case underwent auto-SCT twice with high-dose chemotherapy.

obstruction, gastric bleeding, PV obstruction, and refractory ascites. Five of the 23 patients (21.7%) who underwent hepaticojejunostomy developed biliary complications, as did 5 of the 16 patients (31.3%) who underwent duct-to-duct anastomosis did. Five of the 15 patients (33.3%) who had undergone hepatectomy before LDLT developed biliary complications, and 5 of the 24 cases (20.8%) without hepatectomy before LDLT also developed complications. Eight patients (20.5%) died during the follow-up period, although none of them lost their grafts because of surgical complications. In terms of toxicities related to chemotherapy, 3 patients among the long-term survivors developed mild renal dysfunction (cases 12, 34, and 39), and 1 patient

TABLE 2. Patient Characteristics at LDLT and Patient Outcomes

Case Number	Age at LDLT (Years)	AFP at LDLT (ng/mL)	Donor Age (Years)	Graft Type	Surgical Complications	Histopathological Type of HB	Histological Vascular Invasion (Site)	Chemotherapy	Tumor Recurrence (Interval After LDLT)	Outcomes (Follow-Up Period in Years)
1	10.6	23	38	LLS	No	Fetal	No	CPA	No	Alive (15.2)
2	0.8	4390	35	LLS	No	Macrotrabecular	Yes (HV)	CPA	Lung, skin (5 months)	Died (0.6)
3	7.5	54,700	37	LLS	No	Embryonal	Yes (PV, HV)	CBDCA + VP-16 + CPA*	Lung, graft, diaphragm, central nervous system (2.8 years)	Died (3.4)
4	2.6	5749	27	LLS	Biliary leakage, gastric bleeding	Embryonal	Yes (PV, HV)	CBDCA + VP-16	Lung (3 months)	Died (0.9)
5	4.6	12,924	30	LLS	No	Embryonal	Yes (PV)	CBDCA + THP-ADR	No	Alive (12.5)
6	11.0	383	47	LLS	No	Fetal	No	CBDCA + VP-16	No	Alive (11.8)
7	3.0	10	40	LLS	PV obstruction	Fetal	No	CITA	No	Alive (11.5)
8	5.3	37	29	LLS	Intra-abdominal bleeding	Combined	Yes (PV)	None	No	Alive (10.6)
9	6.9	1411	32	LL	Biliary stricture	Embryonal	Yes (PV)	None	No	Alive (9.2)
10	4.0	7040	25	LLS	Biliary stricture	Embryonal	Yes (PV, HV)	CITA	No	Alive (8.6)
11	5.3	4930	32	LLS	No	Embryonal	Yes (PV, HV)	CITA/ CPT-11	Lung, graft, PD (7 months)	Died (3.1)
12	12.4	113	40	LL	Biliary stricture	Fetal	Yes (PV, HV)	CBDCA + VP-16	No	Alive (7.6)
13	3.9	170,910	31	LLS	Bowel perforation	Embryonal	Yes (PV, HV)	CPT-11/ CPA	Lung, graft (1 month)	Died (0.5)
14	9.1	12	44	LLS	Biliary leakage	Fetal	Yes (PV)	CPT-11	No	Alive (7.4)
15	0.9	7008	41	Reduced LLS	Biliary stricture	Combined	Yes (PV)	CPT-11	No	Alive (6.6)
16	1.3	40	33	LLS	No	Fetal	No	CBDCA + THP-ADR	No	Alive (5.9)
17	4.7	1,175,690	29	LLS	No	Combined	Yes (PV, HV)	CPT-11	Lung (10 months)	Alive (6.5)
18	2.3	136,840	39	LLS	No	Unknown	No	None	No	Alive (6.1)
19	2.0	4264	32	LLS	Biliary stricture	Combined	Yes (PV)	CPT-11	No	Alive (6.1)
20	12.1	1471	44	LLS	Biliary stricture	Combined	No	CPT-11	No	Alive (6.0)

TABLE 2. *Continued*

Case Number	Age at LDLT (Years)	AFP at LDLT (ng/mL)	Donor Age (Years)	Graft Type	Surgical Complications	Histopathological Type of HB	Histological Vascular Invasion (Site)	Chemotherapy	Tumor Recurrence (Interval After LDLT)	Outcomes (Follow-Up Period in Years)
21	0.9	3155	23	LLS	Refractory ascites	Combined	No	None	No	Alive (5.9)
22	14.7	153	40	LL	Biliary stricture	Fetal	No	CPT-11	No	Alive (5.7)
23	3.6	93,000	34	LLS	Intra-abdominal bleeding	Embryonal	Yes (PV)	ITEC	Lung (4 months)	Alive (5.0)
24	7.5	616	31	LLS	No	Fetal	No	CPT-11	No	Alive (4.7)
25	1.1	1,061,480	29	LLS	Biliary stricture	Combined	Yes (PV)	CPT-11	Graft, PD (1.3 years)	Died (1.6)
26	2.5	1331	35	LLS	No	Mixed	No	None	No	Alive (4.6)
27	1.5	67,078	31	Reduced LLS	No	Combined	Yes (PV, HV)	ITEC/ CPT-11/CITA†	Diaphragm (3 months)	Died (0.9)
28	7.1	21,938	34	LLS	No	Macrotrabecular	Yes (PV)	CPT-11†	Graft, PD, systemic lymph nodes (1.1 years)	Died (1.3)
29	3.0	19,740	64	LL	No	Combined	Yes (PV, HV)	None	No	Alive (3.6)
30	3.7	617,900	25	LLS	No	Macrotrabecular	Yes (PV, HV)	CPT-11*	Lung, graft (2 months)	Alive (3.5)
31	1.7	50	38	LLS	Bowel obstruction	Fetal	No	CPT-11	No	Alive (2.8)
32	2.4	331	30	LLS	No	Macrotrabecular	Yes (PV, HV)	CPT-11	Lung (6 months)	Alive (2.6)
33	2.9	1919	45	LLS	No	Embryonal	Yes (PV)	CITA	No	Alive (2.4)
34	22.1	48	54	LL	Intra-abdominal bleeding	Fetal	No	CPT-11	No	Alive (2.2)
35	6.7	12,112	46	LLS	Intra-abdominal bleeding	Combined	No	CPT-11	No	Alive (2.0)
36	3.6	32	26	LL	No	Fetal	No	None	No	Alive (1.6)
37	2.0	1871	27	LLS	No	Combined	Yes (HV)	CPT-11	No	Alive (1.5)
38	1.4	278	30	LLS	No	Fetal	No	ITEC	No	Alive (1.4)
39	1.3	161,476	38	LLS	No	Fetal	Yes (PV, HV)	CITA	No	Alive (1.3)

*The case underwent auto-SCT with high-dose chemotherapy.
†The case underwent bone marrow transplantation.

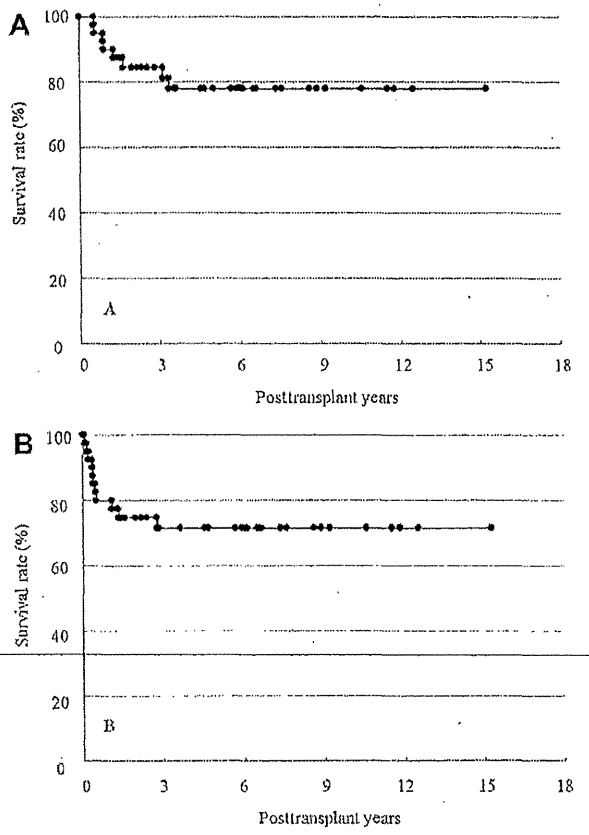

Figure 2. (A) Overall patient survival rate and (B) tumor recurrence-free survival rate.

developed mild auditory impairment (case 24). The overall survival rates were 84.3%, 77.3%, and 77.3% at 3, 5, and 10 years, respectively (Fig. 2A).

Histopathological Examination of the Explanted Liver

The histopathological type of HB in the explanted liver could not be determined in 1 case because of missing data; the rest were the fetal type in 13 cases (34.2%), the combined fetal and embryonal type in 11 cases (28.9%), the embryonal type in 9 cases (23.7%), the macrotrabecular type in 4 cases (10.5%), and a mixed epithelial and mesenchymal type in 1 case (2.6%). Twenty-four cases (61.5%) showed vascular invasion, including invasion into both the PVs and the hepatic veins (HVs) in 12 cases, the PVs in 10 cases, and the HVs in 2 cases.

Details of Tumor Recurrence After LDLT

Postoperative chemotherapy was performed for 32 cases (82.1%). CPT-11 was used as the initial post-transplant chemotherapy in 16 cases; this was followed by CITA in 5 cases, CBDCA and VP-16 in 4 cases, ITEC in 3 cases, CBDCA and THP-ADR in 2 cases, and cyclophosphamide in 2 cases. Postoperative chemotherapy was started at a median of 34 days (range = 0-203 days); this was dependent on the patient's postoperative condition.

Twelve cases (30.8%), all of whom received postoperative chemotherapy, showed tumor recurrence. The median interval between LDLT and the onset of tumor recurrence was 5.2 months (range = 1 month to 2.8 years). The most common site of tumor recurrence was the lung (9 cases), which was followed by the hepatic graft (6 cases), peritoneal dissemination (PD; 3 cases), the diaphragm (2 cases), the skin (1 case), multiple lymph nodes (1 case), and meningeal dissemination (1 case). Four of the 9 cases (44.4%) with lung metastasis underwent surgical resection, and 3 were alive without any tumor recurrence (cases 17, 23, and 32). Two of the 6 patients (33.3%) with tumor recurrence within the hepatic graft underwent surgical resection and radiofrequency ablation, respectively. Although the cases with tumor recurrence received additional systemic chemotherapy, including auto-SCT in 2 cases (cases 3 and 30) and bone marrow transplantation in 2 cases (cases 27 and 28), after they had undergone high-dose chemotherapy, 8 of the 12 cases (66.7%) died because of tumor recurrence, which included complications related to bone marrow transplantation as a direct cause of death (case 27); the median interval from the onset of tumor recurrence was 6 months, with the period ranging from 2 months to 2.6 years. The recurrence-free survival rates were 76.9%, 68.3%, and 68.3% at 1, 3, and 5 years, respectively (Fig. 2B).

Prognostic Factors for Tumor Recurrence After LDLT (Tables 3 and 4)

A univariate log-rank test for identifying the prognostic factors for tumor recurrence revealed that an AFP level at diagnosis $\geq$ 500,000 ng/mL, the presence of extrahepatic lesions before LDLT, a donor age $\leq$ 39 years, an AFP level at LDLT $\geq$ 4000 ng/mL, the histopathological type of HB, and histopathological vascular invasion were significantly associated with a higher incidence of tumor recurrence after LDLT. Although the AFP levels at diagnosis and LDLT were significant prognostic factors, the rate of the decline in the AFP level during the period from the diagnosis to LDLT did not reach statistical significance as a prognostic factor. The episodes of hepatectomy before LDLT (so-called rescue LDLT) were not a significant prognostic factor. The multivariate landmark analysis also showed that the independent risk factors for recurrence were a high AFP level at diagnosis (HR = 7.86, $P = 0.010$), the presence of extrahepatic lesion(s) before LDLT (HR = 3.82, $P = 0.042$), and a high AFP level at LDLT (HR = 9.19, $P = 0.036$).

DISCUSSION

Multicenter trials for HB, conducted by the Children's Oncology Group and the Childhood Liver Tumour Strategy Group of the International Society of

TABLE 3. Prognostic Factors for Recurrence Identified by the Univariate Analysis

Characteristic	n (%)	Recurrence-Free Survival Rate (%)		P Value*
		1 Year	3 Years	
Age at diagnosis				
<2 years old	18 (46.2)	77.8	71.8	0.75
≥2 years old	21 (53.8)	76.2	65.5	
Sex				
Male	28 (71.8)	75.0	66.3	0.82
Female	11 (28.2)	81.8	72.7	
PRETEXT stage				
IV	22 (56.4)	72.7	63.3	0.28†
III	15 (38.5)	80.0	80.0	
II	1 (2.6)	100.0	0.0	
I	1 (2.6)	100.0	N/A	
AFP at diagnosis				
<500,000 ng/mL	22 (56.4)	90.9	90.9	<0.01
≥500,000 ng/mL	17 (43.6)	58.8	41.2	
Extrahepatic lesion(s)				
Yes	13 (33.3)	53.8	46.2	0.01
No	26 (66.7)	88.9	76.8	
Factor‡				
V	1 (7.7)	0.0	N/A	0.02
P	3 (23.1)	33.3	N/A	
E	4 (30.8)	50.0	50.0	
R	2 (15.4)	50.0	N/A	
M	3 (23.1)	66.7	66.7	
Chemotherapy before LDLT				
Number of cycles				
≤6	22 (56.4)	72.7	63.3	0.35
≥7	17 (43.6)	88.2	74.1	
Initial protocol				
CITA	36 (94.7)	75.0	65.5	0.36
Others	2 (5.3)	100.0	100.0	
Transarterial chemoembolization				
Yes	10 (26.3)	70.0	60.0	0.44
No	28 (73.7)	78.6	70.2	
Stem cell transplantation				
Yes	9 (23.7)	77.8	77.8	0.52
No	29 (76.3)	75.9	63.9	
POST-TEXT stage				
IV	22 (62.9)	68.1	58.7	0.20†
III	11 (31.4)	81.8	81.8	
I	2 (5.7)	100.0	N/A	
Liver resection before LDLT				
Yes	15 (38.5)	86.7	78.0	0.24
No	24 (61.5)	70.8	62.2	
Number of resections				
≥2	7 (46.7)	85.7	85.7	0.73
1	8 (53.3)	87.5	72.9	
Period of resection				
Before chemotherapy	3 (20.0)	100.0	50.0	0.58
After chemotherapy	12 (80.0)	83.3	83.3	
Age at LDLT				
<3 years old	17 (43.6)	76.5	70.1	0.92
≥3 years old	22 (56.4)	77.3	67.1	
Interval: diagnosis to LDLT				
<1.5 years	28 (71.8)	71.4	64.1	0.26
≥1.5 years	11 (28.2)	90.9	77.9	
Donor age				
<39 years old	28 (71.8)	67.9	55.9	0.02
≥40 years old	11 (28.2)	100.0	100.0	

TABLE 3. *Continued*

Characteristic	n (%)	Recurrence-Free Survival Rate (%)		*P* Value*
		1 Year	3 Years	
Donor sex				
Male	20 (51.3)	70.0	70.0	0.90
Female	19 (48.7)	84.2	65.2	
Graft type				
LL	6 (15.4)	100.0	100.0	0.23
LLS	31 (79.5)	74.2	63.4	
Reduced LLS	2 (5.1)	50.0	50.0	
ABO-type compatibility				
Compatible	37 (94.9)	75.7	66.7	0.39
Incompatible	2 (5.1)	100.0	100.0	
IVC removal				
Yes (complete or partial)	6 (15.8)	83.3	83.3	0.49
No	32 (84.2)	75.0	64.6	
Immunosuppression at initiation phase				
CNI only	14 (35.9)	85.7	64.3	0.75
CNI with steroids	25 (64.1)	72.0	72.0	
AFP at LDLT				
<4000 ng/mL	20 (51.3)	95.0	95.0	< 0.01
≥4000 ng/mL	19 (48.7)	57.8	40.1	
AFP decline rate: diagnosis to LDLT				
Log-1 decline				
Yes	27 (69.2)	81.5	77.8	0.08
No	12 (30.8)	66.7	45.7	
Log-2 decline				
Yes	17 (43.6)	82.4	82.4	0.14
No	22 (56.4)	72.7	57.0	
ACR				
Yes	13 (33.3)	69.2	51.3	0.20
No	26 (66.7)	80.8	76.9	
Surgical complications				
Yes	18 (46.2)	83.3	77.8	0.33
No	21 (53.8)	71.4	59.3	
Histological type of HB				
Fetal type	13 (34.2)	100.0	100.0	< 0.01
Embryonal type	9 (23.7)	55.6	41.7	
Combined[§]	11 (28.9)	81.8	72.7	
Mixed[‖]	1 (2.6)	100.0	100.0	
Macrotrabecular	4 (10.5)	25.0	N/A	
Histological vascular invasion				
Yes	24 (61.5)	62.5	48.5	< 0.01
No	15 (38.5)	100.0	100.0	
Site of vascular invasion				
PV	10 (41.7)	90.0	70.0	0.18
HV	2 (8.3)	50.0	N/A	
Both PV and HV	12 (50.0)	41.7	31.3	
Chemotherapy after LDLT				
Yes	32 (82.1)	71.9	61.1	0.07
No	7 (17.9)	100.0	100.0	
Chemotherapy protocol				
CPT-11	16 (50.0)	75.0	62.5	0.97
Others	16 (50.0)	68.8	60.2	

*Log-rank test.
†Only compared between cases with PRETEXT stage III and cases with PRETEXT stage IV.
‡V indicates tumor invasion into the IVC and/or 3 HVs, P indicates tumor invasion into the portal trunk and/or bilateral main portal branches, E indicates tumor invasion into other adjacent organs or lymph node metastasis, R indicates tumor rupture, and M indicates metastasis.
§Combined fetal and embryonal type.
‖Mixed epithelial and mesenchymal type.

TABLE 4. Prognostic Factors for Recurrence Identified by the Multivariate Analysis

Pretransplant Factor	HR	95% CI	*P* Value
AFP at diagnosis			
<500.000 ng/mL	1		
≥500,000 ng/mL	7.86	1.62-38.06	<0.01
AFP at LDLT			
<4000 ng/mL	1		
≥4000 ng/mL	9.19	1.16-73.09	0.04
Extrahepatic lesion(s)			
No	1		
Yes	3.82	1.05-13.93	0.04

Paediatric Oncology (SIOPEL), continue to explore the best therapeutic strategies, and the overall survival rate has increased to nearly 80% in the most recent trials.[18,19] For further improvements of outcomes, the refined protocol provided by each multicenter trial has focused on the therapeutic strategy for high-risk HB, including guidelines for LT.[20] Long-term survival rates ranging from 55% to 100% have now been reported for multiple single-center series over the last 2 decades, which collectively show a median survival rate of approximately 80%.[6] The current study had a 77.3% overall patient survival rate and a 68.3% recurrence-free survival rate at 5 years with a median follow-up period of 4.6 years, and these were acceptable outcomes.

The current study was a retrospective review performed to analyze the outcomes of LDLT for HB, even though our own multicenter protocol (JPLT-1 and JPLT-2) was conducted in parallel as background, and it did not include the guidelines for LT. Furthermore, medical coverage of LT for HB was not approved until April 2008. For these reasons, the current study included cases with unresectable HB, which were treated with multiple sessions of chemotherapy with auto-SCT and/or multiple surgical resections before LDLT. Otte et al.[5] has demonstrated that survival with primary LT is significantly superior to survival with rescue LT according to data gathered from experienced transplant centers worldwide. Rescue LT is indicated for cases with incomplete tumor resection and/or intrahepatic recurrence after partial liver resection. It can be reasonably presumed that PRETEXT stage III or IV tumors are likely to be in close proximity to the main vessels, and this can lead to incomplete tumor resection. Even when the resection margins are macroscopically negative for a tumor in a specimen, microscopic residual tumors may be present at the resection line. Tumors that recur after liver resection with adequate chemotherapy may be a more aggressive type of tumor within the spectrum of behavior.[6,21] Therefore, primary LT can be recommended to prevent any attempt at liver resection when radical resection seems difficult.[5,22] On the other hand, a recent report by Lautz et al.[23] revealed excellent outcomes after aggressive resection in children with HB involving 3 or 4 sectors of the liver after neoadjuvant chemotherapy. They recommended careful consideration of all information available before one chooses primary LT or liver resection for cases with likely unresectable HB on a case-by-case basis because LT is not without morbidity and mortality. Furthermore, we have to heavily rely on living donors as an organ resource in our country, and avoiding LDLT for a patient who may have a chance to be cured by liver resection would, therefore, be preferable. The current study did not show inferior outcomes for rescue LT in comparison with primary LT, although the high proportion of cases undergoing liver resection without the option of primary LT at the same time should be taken into consideration. The current JPLT-3 protocol study, which includes surgical guidelines compatible with international validated guidelines (eg, SIOPEL[24]), is trying to draw a definite conclusion for this issue.

The current study showed that serum AFP levels at the time of diagnosis and at LDLT were significant prognostic factors related to tumor recurrence in both univariate and multivariate analyses despite the limitations associated with the retrospective nature of the analysis and the small sample size. A couple of reports have highlighted the possible negative influence of a very high AFP level on outcomes.[25,26] Because the clinical behavior, the presence of extrahepatic lesions before LDLT, the histopathological features of the tumor, the histopathological type, and histopathological vascular invasion were also significant prognostic factors related to tumor recurrence, the serum AFP level at diagnosis can predict outcomes after LDLT as an indicative parameter of the biological nature of the tumor. On the other hand, the serum AFP level at LDLT might be related to the quantitative burden of the residual tumor after pretransplant treatment because microscopic tumor dissemination can occur during the total hepatectomy procedure. Previous studies have revealed that patients with a good response to preoperative chemotherapy have better outcomes after LT in comparison with those with a poor response,[22,27] although the rate of decline in the AFP level during the period from diagnosis to LDLT did not reach statistical significance as a prognostic factor in the current study. This difference from the previous studies may be due to the pretransplant clinical course, which was affected by the various therapeutic modalities before LDLT. The serial changes in the AFP levels of the cases receiving chemotherapy only before LDLT can be differently interpreted from those of the cases with tumor recurrence after liver resections.

One-third of the patients in the current study had extrahepatic lesions before LDLT. Among them, the cases showing direct invasion into the IVC or the adjacent organs (stomach and transverse colon) at the time of LDLT developed tumor recurrence at a relatively early time point after LDLT. There is no doubt that LT is contraindicated for cases showing direct

tumor invasion at the time of LDLT. The cases with a macroscopic tumor thrombus within the PV at LDLT also had a high incidence of tumor recurrence after LDLT in the current study, as previous series similarly reported.[28] One of the 3 cases experienced a disappearance of the tumor thrombus after neoadjuvant chemotherapy and did not exhibit any tumor recurrence, and both of the other cases with remaining macroscopic tumor thrombi at the time of LDLT survived for relatively long periods after LDLT because the sites of recurrence could be managed by surgical resection. With respect to microscopic venous invasion, the existence of tumor invasion in the HVs might be a more significant risk factor for tumor recurrence than invasion in the PVs. The present data suggest that LT can be considered for cases with a macroscopic tumor thrombus within the PV, whereas those with macroscopic venous invasion in the major HVs and the IVC may be considered to have a relative contraindication for LT.

The presence of pulmonary metastasis at diagnosis still remains controversial with respect to indications for LT. It is obvious that LT should be considered for cases with pulmonary metastasis when the pulmonary lesions disappear after chemotherapy. One of the 3 cases in the current study experienced recurrence after LDLT, and the recurrent tumor developed at a site in the left pulmonary lobe similar to the site at which the pulmonary metastasis had been observed at diagnosis (case 32; Y. Inomata, Kumamoto University, written communication, 2013). Therefore, even when metastatic lesions radiologically disappear after chemotherapy, microscopic tumor foci may still remain. The questions remain whether pulmonary metastases can persist after chemotherapy, whether they can be surgically resected, and whether the patients should subsequently be eligible for LT. One patient in our series, who underwent the surgical resection of 4 pulmonary lesions before LDLT, did not show tumor recurrence for 3.5 years after LDLT. That case received high-dose chemotherapy with auto-SCT and then underwent LDLT (case 29; T. Yagi, Okayama University, personal communication, 2013). Because such pulmonary lesions are probably more chemotherapy-resistant, more aggressive chemotherapy with stem cell transplantation may represent an effective therapeutic option that can be given before LT. On the basis of the results of the SIOPEL-1 study, which revealed long-term recurrence-free survival for 4 of 5 patients (80%) with pulmonary metastases at the time of diagnosis, Otte et al.[5,29] suggested that LT might be considered for cases with pulmonary metastases with a paramount prerequisite of complete eradication by chemotherapy and/or surgical resection. This requires meticulous scrutiny of the lungs before LT by high-resolution radiological modalities.[6]

The management of patients after LT, including the immunosuppression regimen and chemotherapy, is also still controversial. Our series included 14 cases treated with a steroid-free regimen because of the presumption of a high risk of infections and tumor recurrence.[8] There were no significant differences among the patients treated with different types of immunosuppression in terms of tumor recurrence and infections, and the incidence of ACR was not higher than the standard incidence of ACR after LDLT.[30] Although detailed data, such as the target trough levels of immunosuppressants, were not obtained, the immunosuppression regimen could be considered to be standard.

A recent report from Wagner et al.[31] showed that rapamycin effectively inhibited HB growth in both in vitro and in vivo studies. The potential benefits of other types of immunosuppressants with antitumorigenic properties, such as rapamycin, require further evaluation. The use of postoperative chemotherapy remains an open debate. Seven cases in the present series did not undergo chemotherapy after LDLT, and they did not show any tumor recurrence. No specific characteristic related to the clinical and laboratory data before and after LDLT could be found, and the consideration about the necessity of postoperative chemotherapy was left to each center's discretion. We believe that postoperative chemotherapy should be considered for cases with extrahepatic lesions before LT, including macroscopic/microscopic vascular invasion, which was clearly defined as a significant prognostic factor for tumor recurrence. The selection of the chemotherapy regimen after LT should be based on the effectiveness for the tumor and the side effects of the preoperative chemotherapy regimen. A recent report revealed that CPT-11 had significant antitumor activity and acceptable toxicity in patients with relapsed HB.[32] Half of the cases in our series were treated with CPT-11 as postoperative chemotherapy, although this agent did not show any significant superiority in terms of recurrence-free survival. Further prospective studies of postoperative chemotherapy are needed.

In conclusion, a nationwide survey of the outcomes of LDLT for HB in Japan, in which 39 patients were enrolled, showed excellent results. A multivariate analysis revealed that the independent risk factors for recurrence were a high AFP level at diagnosis (500,000 ng/mL), the presence of extrahepatic lesions before LDLT, and a high AFP level at LDLT (4000 ng/mL). With respect to extrahepatic lesions before LDLT, the presence of macroscopic venous invasion and viable extrahepatic lesions not amenable to surgical excision should be a contraindication for LT. However, the current retrospective study included cases with different backgrounds with respect to therapeutic decisions before and after LDLT for a relatively long study period. Further investigations through the nationwide management protocol (conducted by the JPLT) may clarify the precise indications for LT as a treatment for HB.

ACKNOWLEDGMENT

The authors deeply thank the Japanese Study Group for Pediatric Liver Tumor (Hiroshima, Japan) and its

representative, Dr. Eiso Hiyama, and the following transplant institutions for their cooperation with the current study: Hokkaido University, Jichi Medical University, Tokyo Women's Medical University, Keio University, Nagoya University, Fujita Health University, Kanazawa Medical University, Kyoto University, Osaka University, Nara Medical University, Okayama University, Kyushu University, Kumamoto University, and the National Center for Child Health and Development.

REFERENCES

1. Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992-2004). Cancer 2008;112:416-432.
2. Allan BJ, Parikh PP, Diaz S, Perez EA, Neville HL, Sola JE. Predictors of survival and incidence of hepatoblastoma in the paediatric population. HPB (Oxford) 2013;15:741-746.
3. Gupta AA, Gerstle JT, Ng V, Wong A, Fecteau A, Malogolowkin MH, et al. Critical review of controversial issues in the management of advanced pediatric liver tumors. Pediatr Blood Cancer 2011;56:1013-1018.
4. Héry G, Franchi-Abella S, Habes D, Brugières L, Martelli H, Fabre M, et al. Initial liver transplantation for unresectable hepatoblastoma after chemotherapy. Pediatr Blood Cancer 2011;57:1270-1275.
5. Otte JB, Pritchard J, Aronson DC, Brown J, Czauderna P, Maibach R, et al.; for International Society of Pediatric Oncology (SIOP). Liver transplantation for hepatoblastoma: results from the International Society of Pediatric Oncology (SIOP) study SIOPEL-1 and review of the world experience. Pediatr Blood Cancer 2004;42:74-83.
6. Meyers RL, Czauderna P, Otte JB. Surgical treatment of hepatoblastoma. Pediatr Blood Cancer 2012;59:800-808.
7. Tanaka K, Uemoto S, Tokunaga Y, Fujita S, Sano K, Nishizawa T, et al. Surgical techniques and innovations in living related liver transplantation. Ann Surg 1993;217:82-91.
8. Kasahara M, Ueda M, Haga H, Hiramatsu H, Kobayashi M, Adachi S, et al. Living-donor liver transplantation for hepatoblastoma. Am J Transplant 2005;5:2229-2235.
9. Hishiki T, Matsunaga T, Sasaki F, Yano M, Ida K, Horie H, et al. Outcome of hepatoblastomas treated using the Japanese Study Group for Pediatric Liver Tumor (JPLT) protocol-2: report from the JPLT. Pediatr Surg Int 2011;27:1-8.
10. Suita S, Tajiri T, Takamatsu H, Mizote H, Nagasaki A, Inomata Y, et al.; for Committee for Pediatric Solid Malignant Tumors in the Kyushu Area, Japan. Improved survival outcome for hepatoblastoma based on an optimal chemotherapeutic regimen—a report from the Study Group for Pediatric Solid Malignant Tumors in the Kyushu Area. J Pediatr Surg 2004;39:195-198.
11. Matsunaga T, Sasaki F, Ohira M, Hashizume K, Hayashi A, Hayashi Y, et al.; for Japanese Study Group for Pediatric Liver Tumor. Analysis of treatment outcome for children with recurrent or metastatic hepatoblastoma. Pediatr Surg Int 2003;19:142-146.
12. Ozawa K, Uemoto S, Tanaka K, Kumada K, Yamaoka Y, Kobayashi N, et al. An appraisal of pediatric liver transplantation from living relatives. Initial clinical experiences in 20 pediatric liver transplantations from living relatives as donors. Ann Surg 1992;216:547-553.
13. Hashikura Y, Kawasaki S, Terada M, Ikegami T, Nakazawa Y, Urata K, et al. Long-term results of living-related donor liver graft transplantation: a single-center analysis of 110 transplants. Transplantation 2001;72:95-99.
14. Egawa H, Oike F, Buhler L, Shapiro AM, Minamiguchi S, Haga H, et al. Impact of recipient age on outcome of ABO-incompatible living-donor liver transplantation. Transplantation 2004;77:403-411.
15. Demetris A, Adams D, Bellamy C, Blakolmer K, Clouston A, Dhillon AP, et al. Update of the international Banff schema for liver allograft rejection: working recommendations for the histopathologic staging and reporting of chronic rejection. An international panel. Hepatology 2000;31:792-799.
16. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-387.
17. Tsuruta H, Bax L. Polychotomization of continuous variables in regression models based on the overall C index. BMC Med Inform Decis Mak 2006;6:41.
18. Zsíros J, Maibach R, Shafford E, Brugieres L, Brock P, Czauderna P, et al. Successful treatment of childhood high-risk hepatoblastoma with dose-intensive multiagent chemotherapy and surgery: final results of the SIOPEL-3HR study. J Clin Oncol 2010;28:2584-2590.
19. Perilongo G, Malogolowkin M, Feusner J. Hepatoblastoma clinical research: lessons learned and future challenges. Pediatr Blood Cancer 2012;59:818-821.
20. Meyers RL, Tiao GM, Dunn SP, Langham MR Jr, Liver transplantation in the management of unresectable hepatoblastoma in children. Front Biosci (Elite Ed) 2012;4:1293-1302.
21. Browne M, Sher D, Grant D, Deluca E, Alonso E, Whitington PF, Superina RA. Survival after liver transplantation for hepatoblastoma: a 2-center experience. J Pediatr Surg 2008;43:1973-1981.
22. Pimpalwar AP, Sharif K, Ramani P, Stevens M, Grundy R, Morland B, et al. Strategy for hepatoblastoma management: transplant versus nontransplant surgery. J Pediatr Surg 2002;37:240-245.
23. Lautz TB, Ben-Ami T, Tantemsapya N, Gosiengfiao Y, Superina RA. Successful nontransplant resection of POST-TEXT III and IV hepatoblastoma. Cancer 2011;117:1976-1983.
24. Czauderna P, Otte JB, Aronson DC, Gauthier F, Mackinlay G, Roebuck D, et al.; for Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). Guidelines for surgical treatment of hepatoblastoma in the modern era—recommendations from the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). Eur J Cancer 2005;41:1031-1036.
25. von Schweinitz D, Hecker H, Schmidt-von-Arndt G, Harms D. Prognostic factors and staging systems in childhood hepatoblastoma. Int J Cancer 1997;74:593-599.
26. Maibach R, Roebuck D, Brugieres L, Capra M, Brock P, Dall'Igna P, et al. Prognostic stratification for children with hepatoblastoma: the SIOPEL experience. Eur J Cancer 2012;48:1543-1549.
27. Cruz RJ Jr, Ranganathan S, Mazariegos G, Soltys K, Nayyar N, Sun Q, et al. Analysis of national and single-center incidence and survival after liver transplantation for hepatoblastoma: new trends and future opportunities. Surgery 2013;153:150-159.
28. Reyes JD, Carr B, Dvorchik I, Kocoshis S, Jaffe R, Gerber D, et al. Liver transplantation and chemotherapy for hepatoblastoma and hepatocellular cancer in childhood and adolescence. J Pediatr 2000;136:795-804.