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Benefit of early inflow exclusion during living donor liver transplantation for unresectable hepatoblastoma☆

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ABSTRACT

Background: Hepatoblastoma (HB) is a highly malignant primary liver tumor in children. Although liver transplantation (LT) is an effective treatment for unresectable HB with good long-term outcomes, post-transplant survival is mainly affected by recurrence, despite adjuvant chemotherapy. Novel strategies are needed to improve the outcomes in patients undergoing LT for unresectable HB.

Patients and methods: Twelve children received LT for unresectable HB. In 9 patients, we applied early exclusion of hepatic inflow (hepatic artery and portal vein) and creation of a temporary portocaval shunt during LT.

Result: There were differences in the duration of and the blood loss during operation as compared with previously reports. The estimated glomerular filtration rate was well preserved at 3, 6, and 12 months and the latest follow-up after LT, and the recurrence-free survival was 88.9%.

Conclusion: Early inflow control during LT for unresectable HB may benefit recurrence-free survival by minimizing blood loss and tumor dissemination, preserving renal function and allowing early adjuvant chemotherapy.

Hepatoblastoma (HB), which is the most common primary malignant liver tumor in children, is usually diagnosed in the first few years of life [1]. Complete surgical resection with effective chemotherapy is essential for treatment with curative intent. With the evolution of systemic cisplatin-based neoadjuvant chemotherapy (NAC), and the ability to achieve complete surgical resection, even in advanced tumors; the overall survival has improved to more than 80% [2–4]. However, approximately 20% of HBs are deemed unresectable, even after NAC [5]. For unresectable HB, there have been encouraging reports from multicenter registries of 80% long-term survival with a combination of NAC followed by liver transplantation (LT) [3,6,7]. Nonetheless, tumor recurrence, particularly pulmonary metastasis, which is the most common type of extrahepatic recurrence, may be unavoidable. According to a Japanese registry the recurrence-free survival rates after LT were 76.9% and 68.3% at 1 and 3 years, respectively [8–10].

Regarding hepatocellular carcinoma (HCC), it is well known that operative manipulation, increased intraoperative blood loss and blood transfusions are potential mechanisms in the pathogenesis of postoperative tumor recurrence [11–13]. The concept of inflow occlusion as a means to reduce intraoperative blood loss in hepatic malignancies is not unknown [14]. We utilized and extended this concept of inflow control as an early step during total hepatectomy and LT for unresectable HB. Furthermore, measures to reduce intraoperative blood loss and maintain hemodynamic stability during total hepatectomy and LT (including temporary portocaval shunt – TPCS) may result in better preservation of postoperative renal function [15–19]. This may allow the early use of full-dose adjuvant chemotherapy (ACT) after LT.

We herein, review the overall outcomes of all patients with unresectable HB at our center, and focus on the patients who underwent

Abbreviations: ACT, adjuvant chemotherapy; ACR, acute cellular rejection; AFP, alpha-fetoprotein; CDDP, cisplatin; CPT-11, irinotecan; eGFR, estimated glomerular filtration rate; HB, hepatoblastoma; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; LT, liver transplantation; NAC, neoadjuvant chemotherapy; PRETEXT, pretreatment extent of disease; POSTEXT, posttreatment extent of disease; TPCS, temporary portocaval shunt.

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Table 1
Patient characteristics before LDLT.

Patient	Age at diagnosis (years)	Sex	PRETEXT stage	AFP at diagnosis (ng/ml)	Extrahepatic involvement (Site)	Total dose of cisplatin (mg/m^2)	eGFR at LDLT ($ml/min/1.73m^2$)	POSTTEXT stage	Resection before LDLT (site)
1	0.2	F	III	417,000	No	480	83.5	III	No
2	1.1	F	IV	1,651,000	Lung	560	60.8	IV	No
3	1.5	M	IV	260,360	No	330	197.5	III	No
4	1.5	M	III	403,730	No	640	74.9	III	No
5	1.8	F	III	463,981	No	480	92.3	III	No
6	2.2	F	III	1,129,717	No	640	141.2	III	Liver
7	2.6	M	IV	1,087,000	Lung	570	122.9	IV	No
8	2.7	F	IV	78,183	Rupture	240	113.3	III	No
9	6.9	M	IV	866,000	Rupture	80	176.1	IV	No
10	1.6	M	IV	566,725	Rapture	400	130.7	IV	Liver, Lung
11	2.1	M	IV	584,289	No	240	80.3	IV	No
12	2.5	M	III	692,673	No	600	102.0	III	Lung

LDLT with the early exclusion of hepatic inflow (hepatic artery and PV) and TPCS.

1. Patients and methods

A total of 375 liver transplantations were performed between November 2005 and November 2015 at the National Center for Child Health and Development, Tokyo, Japan. Twelve patients (3.2%) required LT for unresectable HB. Of these patients, 9 (4 male) received LDLT with the early exclusion of inflow and TPCS. Three patients were excluded from the study because of PV thrombosis ($n = 1$) and suspected tumor invasion of the PV or inferior vena cava (IVC) ($n = 2$). The median age at diagnosis was 1.8 years (range: 0.2–6.9 years). The median serum alpha-fetoprotein (AFP) level at the time of diagnosis was 463,981 ng/ml (range: 78,183–1,651,000 ng/ml). According to the pretreatment extent of disease (PRETEXT) staging system, 4 patients (44.4%) were PRETEXT III and 5 patients (55.6%) were PRETEXT IV (Table 1). Four patients had extrahepatic involvement at the time of diagnosis. Two patients had an episode of tumor rupture (patients 8 and 9) and two patients showed lung metastasis (patients 2 and 7). All 9 patients were diagnosed with an unresectable HB and NAC was administered according to the Japanese Study Group for Pediatric Liver Tumor protocol-2 (JPLT-2) and/or the Childhood Liver Tumors Strategy Group (SIOPEL) protocol [20–22]. The median total dose of cisplatin (CDDP) before LDLT was 480 mg/m^2 (range: 80–640 mg/m^2) and the median estimated glomerular filtration rate (eGFR) at LDLT was 113.3 $ml/min/1.73m^2$ (range, 60.8–197.5 $ml/min/1.73m^2$). Three patients had mild renal dysfunction, which was categorized as chronic kidney disease (stage 2; patients 1, 2 and 4). Radiologically, the extrahepatic lesions disappeared in all patients after chemotherapy and the posttreatment extent of disease (POSTEXT) was III in 6 patients (66.7%) and IV in 3 patients (33.3%). Eight patients underwent primary LDLT, while patient 6 underwent hepatectomy before LDLT. The median interval between diagnosis with HB and LDLT was 12 months (range: 6–44 months). As reference, characteristics of excluded patients before LDLT are also shown in Table 1 (patient 10–12).

1.1. Surgical procedure

We started with the recipient first. Complete exploration of the abdominal cavity was performed to exclude any extrahepatic abdominal tumor and confirm the negative cytology of the peritoneal fluid. Intraoperative ultrasound Doppler was performed to further confirm that the HB was not amenable to conventional liver resection, including the tumor invasion of PV and IVC. Only after confirmation of the operability and the need for LT in the recipient, the donor was brought to operating room for liver donation operation. The recipient operation proceeded as follows.

At first, the hepatic hilum was dissected to isolate the structures. The common bile duct and hepatic artery were ligated and divided. The PV was clamped and divided. The IVC was exposed along the retro/infrahepatic space. The exposed IVC was side-clamped and end-to-side TPCS was constructed. The unclamping of the PV and IVC established blood flow through the shunt. Thereafter, the triangular ligament and the gastrohepatic ligament were opened. Then, the liver was rolled to the left to a minimum; short hepatic veins were ligated and the hepatic vein was isolated and divided while checking the flow of TPCS. Total hepatectomy was completed. After removal of the native liver, TPCS was divided and closed using a running suture. Implantation of the graft employed a standard piggy-back LDLT technique.

1.2. Postoperative management

The basic immunosuppressive regimen consisted of tacrolimus and low-dose steroids in all cases.

ACT was started depending on the patient's general condition, especially their liver and renal function. Patients with a good response to NAC received the same postoperative chemotherapy regimen. For those with a poor response to NAC (7 patients), irrinotecan (CPT-11) was used as an ACT [23,24].

2. Results

Table 2 shows patient characteristics at LDLT. The median serum AFP level at the time of LDLT was 730 ng/ml (range: 39–105,922 ng/ml). The median age and body weight at the time of LDLT was 2.2 years (range: 0.6–7.1 years) and 12 kg (range: 9.3–16.2 kg), respectively. The median duration and blood loss of the operation was 360 min (range: 230–616 min) and 29.6 g/kg (range: 19.7–60.8 g/kg), respectively. The median total clamping time of PV was 35 min (range: 25–50 min), including the median time of TPCS reconstruction of 9 min (range: 2–13 min) and warm ischemic time of 24 min (range: 23–39 min). The median time between the establishment of TPCS and removal of the native liver was 34 min (range: 15–68 min). The histology of the explanted liver was examined to determine the HB sub-type (Table 2). There were 7 cases of combined fetal and embryonic type (77.8%), and 1 case each of fetal type and macrotrabecular type (11.1%). Two patients (22.2%) showed vascular invasion into the PV. There were no surgical complications in any of the patients and the postoperative course was uneventful. All patients received ACT; CPT-11 and SIOPEL-4 were used in 7 and 2 patients, respectively. The median eGFR at ACT was 104.2 $ml/min/1.73m^2$ (range: 77.5–142.7 $ml/min/1.73m^2$). ACT was started at a median of 28 days (range: 22–46 days); ACT was delayed in one patient (patient 5) delayed because of cytomegalovirus infection. According to serial assessment of renal function, there was no significant renal impairment in any of the patients after LDLT (Fig. 1). The recurrence-free survival rate was 88.9%. One patient (patient 9) died from tumor recurrence with graft and peritoneal dissemination at 1.1 years after LDLT (Table 3). The median follow-up period is 2.7 years.