described earlier for primary OLT (16). Until September 2000, selective bowl decontamination was used for infection prevention in combination with parenteral antibiotics for 48 h. After that period, only parenteral antibiotics were given for 48 h. In all patients with re-OLTs, intravenous Amphotericine B was added for two wk as prophylaxis for fungal infections. For herpes viral prophylaxis, oral acyclovir was given for four wk.

Antibiotic regimens were adapted when necessary with regard to the renal function of the patient and the colonization status.

The immunosuppressive protocols were the same as described previously (16, 17). Until 1999, immunosuppression in children consisted of triple therapy with cyclosporine A, azathioprine, and prednisolone. After 1999, dual drug immunosuppressive schemes with either cyclosporine A or tacrolimus and low-dose prednisolone have been used in children (17). In adults, immunosuppression consisted of a double scheme with prednisolone, azathioprine, and induction for 10 d with cyclophosphamide until 1986. From 1986 until 1999, a triple immunosuppressive scheme was used that included cyclosporine A, azathioprine, and prednisolone. After 1999, immunosuppression was tailored to the individual needs of the patient. Patients with auto-immune diseases remained on the triple immunosuppressive scheme, however with low-dose steroids. All other patients received a double immunosuppressive scheme including either cyclosporine A or tacrolimus with low-dose steroids. In patients with compromised renal function, induction therapy with IL-2 antibodies was used, and calcineurin inhibitors were only given when creatinine clearance was above 50 mL/min. These basic protocols were used when the interval between the re-OLTs was of such length that the patients had been put on maintenance immunosuppression. In patients receiving several grafts during the same admission, immunosuppression was reduced to the lowest level possible when the decision for re-OLT was made. After the (repeated) re-OLT, immunosuppression was increased to levels similar to those used in first transplantations and was compatible with the overall condition and renal function of the patient.

Only biopsy-proven rejections were treated if clinical and laboratory signs mandated steroid bolus treatment. Steroid-resistant rejections were treated with immunoglobulins (OKT3) during the early period of the study and were switched to tacrolimus more recently.

Post-operative surveillance was done by regular determinations of relevant laboratory parameters, with protocolized liver biopsies at one wk and on demand. A strict Doppler ultrasound protocol was introduced in 1995 to check for the patency of arterial portal and venous anastomosis (18).

Study design

The following study variables from the 23 patients of the study group were retrieved: gender, age, original liver disease, indications for re-OLT, Child-Pugh score at time of the transplantations, and the time interval between the primary and repeated transplantations. Regarding the transplantations, data on blood loss, the duration of the operation, cold ischemic time, revascularization time, graft type, and implantation type were collected. The model for end-stage liver disease (MELD) score was not used in this study as the majority of primary of transplantations were performed before the introduction of the MELD score in the Eurotransplant Area in 2000.

As outcome parameters, the following were recorded: overall patient survival defined as the time period in months between the primary transplantation and patient death, or the end of the observation period (October 26, 2008). To give special attention to the outcome of multiple (second and third) re-OLTs, the outcome of patients and grafts after the second re-OLT was also taken as an end point.

Patient survival after the second re-OLT was defined as the time period (months) between the second re-OLT and death, or the end of the study period. For graft survival, the time period between the second re-OLT and a third re-OLT or patient death, or the end of the study period, was recorded.

Statistical methods

The patient and graft survivals were computed using the Kaplan–Meier method. The log-rank test was used to compare the survival between different groups. Surgical variables were compared with ANOVA, and a p value < 0.05 was considered to be statistically significant.

Results

In Table 2, the indications for the primary and re-OLTs are shown together with information regarding the gender of the patients, their age, Child-Pugh score at the time of the OLTs and the interval, (median and range) between the OLTs. The most frequent indication for primary OLT in adults was acute liver failure (40%). In children, cholestatic disorders (n = 6) and tyrosinemia (n = 5) were the dominant indications. In adults,

Table 2. Demographic, disease-related data and interval data regarding the primary and repeated liver transplantations of the study population

	Primary OLT	First re-OLT	Second re-OLT	Third re-OLT
Indications				
Adults				
1	ALF	Rec. Hep.C	PNF	
2	ALF	CR	HAT[a]	
3	ALF	HAT	HAT	
4	ALF	AR	CR	HAT[a]
5	AIH	CR	CR[a]	
6	PSC	ITBL	ITBL	HAT
7	HBV cirrhosis	AIH	HAT	
8	PSC	ITBL	SBC	HAT
9	AIH	CR	HAT	
10	PBC	ITBL	HAT	
Interval[b]		72 (1–155)	22 (0–149)	1
Gender	M/F: 5/5			
Age	29 (21–55)	32 (23–62)	35 (28–62)	46 (32–55)
C-P Score	9 (5–12)	9 (6–11)	10 (5–13)	11 (5–12)
Children				
1	BA	SBC	SBC	PNF[a]
2	BA	PNF	HAT/PVT	
3	BA	PNF	VOD[a]	
4	BA	HAT	HVO	
5	Tyrosinemia	HAT	HVO	PNF
6	Tyrosinemia	HAT	Fibrosis	
7	Tyrosinemia	EBV	HVO	HAT[a]
8	ALF	SBC	HAT[a]	
9	Alagille	HAT	HAT	
10	SBC	ITBL	HAT/VPT	TF
11	Tyrosinemia	SBC	HAT	
12	Tyrosinemia	HAT	HVO	
13	HCC	HAT	Fibrosis	
Interval[b]		0 (0–112)	0 (0–173)	0
Gender	M/F: 5/8			
Age	2 (0–11)	5 (1–19)	9 (1–19)	6 (1–9)
C-P Score	9 (5–13)*	11 (6–13)	12 (6–15)	13 (12–14)

ALF, acute liver failure; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; BA, biliary atrasia; SBC, secondary biliary cirrhosis; rec HepC, recurrent hepatitis C; HAT, hepatic artery thrombosis; ACR, acute cellular rejection; PNF, primary non function; ITBL, ischemic type biliary lesions; HVO, hepatic vein occulusion; PVT, portal vein thrombosis; TF, technical failure; OLT, orthotopic liver transplantations; re-OLT, orthotopic liver re-transplantations. Data are expressed as median value and range.
[a]Deceased.
[b]Interval in months (median and ranges).
*$p < 0.05$ vs. third re-OLT.

the indication for the first re-OLT showed no specific pattern apart from the fact that only one (8%) indication was acute liver failure, while the other seven were because of chronic conditions. In children, secondary biliary cirrhosis (n = 3), primary non-function (PNF) (n = 2), and hepatic artery thrombosis (n = 5) were the main indications. In adults, the indications for the second re-OLT varied from hepatic artery thrombosis (n = 5), chronic rejection (n = 2), PNF, ischemic type biliary lesions (ITBL), and secondary biliary cirrhosis (n = 1 each). In children, the dominant indication for the second re-OLT was vascular complications, which included hepatic artery thrombosis (n = 3), combined hepatic artery and portal vein thrombosis (n = 2), hepatic venous outflow obstruction (n = 4), graft fibrosis (n = 2), veno-occlusive disease (n = 1), and SBC (n = 1). In adults, the indications for the three third re-OLTs were all hepatic artery thrombosis. One technical failure, and two primary non-functioning grafts and hepatic artery thrombosis were the indications for the third re-OLT in children.

There was a striking difference in the interval between the repeated re-OLT in adults and children. In adults, the interval between primary OLT and repeat transplantations was significantly longer than that in children ($p = 0.018$). However, within each group, there were no differences in the median length of the interval among first, second, and third re-OLTs.

In Fig. 1, the sequence of the repeated re-OLT is depicted. In adults, only one first re-OLT (10%) was performed in the same admission as the primary OLT, whereas in children seven (54%) of the first re-OLTs were performed in the same admission as the primary OLT ($p < 0.05$).

The surgical data are shown in Table 3. In children, the blood loss during the first and second repeat OLTs did differ significantly from that during the primary OLT. In adults, the median length of surgery was longer for second re-OLTs, compared to the primary OLT. In children, the median length of surgery was significantly longer for second re-OLTs, compared to primary and first re-OLT. The median cold ischemic time (for the definition, see the legend for Table 3) and median revascularization time (defined in the legend for Table 3) did not differ in either adults or children between the (re)transplantations. In adults, only full size grafts were used, and these were implanted either conventionally or using the piggy back technique. In children, the majority of the grafts were partial grafts, and all but one split graft were reduced size grafts.

Three adults (30%) died, two after the second re-OLT, and one after the third re-OLT. Four children (31%) died; two after the second re-OLT, and two after the third re-OLT. The absolute overall patient survival was 16 (70%) of 23 patients. The overall actuarial patient survival at 1, 3, 5, and 10 yr after the primary OLT was 96%, 91%, 87%, and 71%, respectively. In adults, the overall actuarial patient survival after primary OLT at these time points was 90%, 90%, 90%, and 64%, respectively, and in children was 92%, 85%, 85%, and 75%, respectively ($p = 0.90$). The overall actuarial 1-, 3-, 5-, and 10-yr survival after the second re-OLT was 78%, 73%, 67%, and 67%,

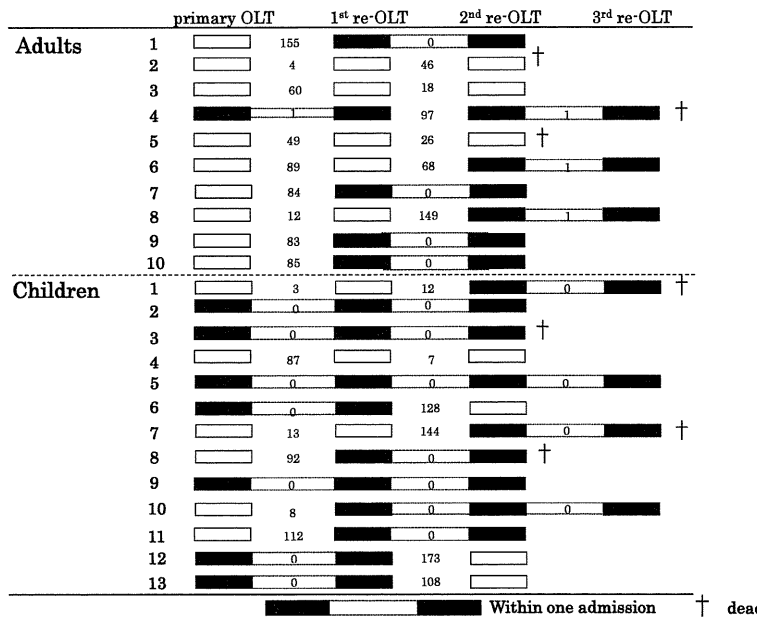

Fig. 1. A schematic presentation of the time interval between each liver transplantation. The combined bars signify orthotopic liver transplantations performed during the same admission. The numbers presented between the bars indicate the number of months between two transplant procedures.

respectively. In adults, the actuarial patient survival after the second re-OLT at 1, 3, and 5 yr was 77%, 68%, and 68%, while it was 80%, 64%, and 64% in children (p = 0.91).

Eleven grafts (48%) were lost after the second re-OLT: four as a result of patient death and seven as a result of graft failure. These grafts were replaced by a third re-OLT. Four grafts survived (57%), and three were lost as a result of the patient's death. The four patients with three re-OLTs were still alive after 124, 80, 48, and 35 months of follow-up, respectively. The results in these 23 patients were obtained at the expense of a total of 76 liver grafts. Thirty-three grafts were used in 10 adults, and 43 grafts were used in 13 children.

Table 3. Operation data of the primary and repeated liver transplantations of the patients with repeated re-OLTs

	Primary OLT (N = 10)	First re-OLT (N = 10)	Second re-OLT (N = 10)	Third re-OLT (N = 3)
Adults				
Blood loss (L)	2.0 (1–30)	3.4 (2.5–10)	2.9 (2.3–17)	8 (3.8–16)
Operation time (min)	489 (350–840)	704 (360–735)	645 (535–915)[a]	515 (480–905)
Cold ischemic time (min)	594 (249–720)	571 (434–786)	530 (315–690)	521 (477–636)
Revascularization time (min)	96 (59–118)	103 (72–141)	97 (75–189)	108 (76–119)
Graft type: full size/partial	10/0	10/0	10/0	3/0
Piggy back/conventional	3/7	6/4	7/3	1/2
	Primary OLT (N = 13)	**First re-OLT (N = 13)**	**Second re-OLT (N = 13)**	**3rd re-OLT (N = 4)**
Children				
Blood loss (L)	0.9 (0.2–4.9)	3.2 (0.4–23)[b]	5.5 (3.5–9)[b]	2.9 (0.6–6)
Operation time (min)	394 (270–835)	435 (261–590)	535 (345–855)[c]	400 (238–555)
Cold ischemic time (min)	553 (360–647)	560 (343–952)	517 (363–900)	451 (409–855)
Revascularization time (min)	87 (49–105)	88 (58–116)	90 (49–140)	77 (74–105)
Graft type: full size/partial	7/6	2/11	4/9	2/2
Piggy back/conventional	8/5	10/3	8/5	1/3

Cold ishchemic time: time until reperfusion with portal venous blood; Revascularization time: time until reperfusion with arterial blood after portal venous reperfusion. OLT, orthotopic liver transplantations; re-OLT, orthotopic liver re-transplantations.
[a]$p < 0.05$ vs. primary OLT in Adults.
[b]$p < 0.05$ vs. primary OLT in Children.
[c]$p < 0.05$ vs. primary and first re-OLT in Children.

Discussion

The sole aim of this study was to report the long-term patient survival data of 23 patients after repeated re-OLT of the liver in a single center. The patients in this series were treated over a 30-yr period, during which medical treatment, donor management and preservation solutions, surgical techniques, radiological and endoscopic diagnostic and intervention techniques, and (last but not least) experience of the team changed considerably. This was especially important with regard to the prevention and treatment of infections, immunosuppressive regimens, and monitoring and treatment of biliary and vascular complications. Moreover, repeated re-OLT often requires aberrant and creative techniques to revascularize the graft. Because of the heterogenity of the data and the small number of patients involved, a meaningful analysis of the available data, other than the descriptive one provided herein, is not possible.

Sixteen patients (70%) of the 23 survived (absolute survival). The overall actuarial patient survival after the primary OLT in the whole series at 1, 3, 5, and 10 yr was 96%, 91%, 87%, and 71%, respectively. After the second re-OLT, 78%, 73%, 67%, and 67% of the patients survived at 1, 3, 5, and 10 yr. After the third re-OLT, four of the seven patients survived. The overall median survival after the primary OLT of the 23 patients was 115 months (range 8–224). Adult patients had a median survival of 109 months (range 50–224), and children had a median survival of 115 months (range 8–204). No differences in survival data were observed between adults and children. The results were obtained at the expense of considerable morbidity and re-interventions (data not shown). From the patients' perspective, these results are rewarding; however, this success was at the cost of 76 grafts for those 23 patients. Two basic questions need to be answered.

First, can such need for repeated re-OLTs be prevented? Looking at the indications for the repeated re-OLTs, vascular causes for previous graft failure were dominant in this series. In adults, seven (54%) of 13 s and third re-OLTs were performed because of vascular complications of the previous graft. In children, 11 (65%) of the second and third reOLTs were performed because of vascular complications in the previous grafts. Single causes for these vascular complications were difficult to identify. Up until 2000, we did not use systemic anticoagulants after transplantation because of the risk of bleeding problems because of blood loss during surgery and a fear for bleeding complications at that time. In addition, patients with specific thrombophylic disorders, such as antiphospholipid syndrome or paroxysmal nocturnal hemoglobinuria [as reported by Vivarelli et al. (19)], were not excluded. Meticulous technique and the use of magnifying loupes, in combination with screening for prothrombotic conditions, and the post-operative use of anticoagulants and close monitoring with Doppler ultrasound as described in several reports, and subsequently adopted in our program, might prevent these complications (18, 20). In addition, the secondary biliary cirrhosis that was an indication for re-OLTs might be preventable. The cirrhosis is often because of stenosis of the biliary anastomosis and the consequent recurrent cholangitis, especially in hepatico jejunostomies (21, 22). In adults, it was the indication for re-OLT in one patient, and in children in three patients (in one child twice). This complication might be prevented with attention to technique, and newer radiological or endoscopic intervention techniques are available to treat such stenoses non-surgically, thus resulting in a substantial chance for preventing secondary cirrhosis (22). PNF was the indication for re-OLT in one adult and in four children. ITBL were the indication for re-transplantation in four adults and in one child. PNF and ITBL are both donor-related and difficult to predict. Careful selection of donors and reducing the cold ischemic times as much as possible might reduce the need for re-OLT because of these conditions. Other indications were unpreventable because of the development of recurrent disease (recurrent fibrosis/cirrhosis, hepatitis C, AIH) or untreatable (therapy-resistant acute and chronic rejections) or bad luck (technical failure).

Recently, Marudanayagam et al. reported that five-yr survival after second re-transplantation was 40% at their institution, while none of their patients have yet survived three yr after a third re-graft, which was inferior to the results of the current study. The authors suggested that a donor age of $\leq$ 55 yr and a MELD score of $\leq$ 23 were associated with a better outcome following re-transplantation. The authors of this study concluded that there was no survival benefit following second and repeat re-OLT. However, their data need further investigation with meta-analysis of the results, as the background of patients undergoing repeat re-OLT was different between their study and the present study.

There is also the ethical question remaining about whether it is justifiable to use 76 grafts for the treatment of 23 patients. From a socio-economic point of view, the question arises whether these scarce organs were used optimally. One might argue that a substantial number of these

Table 4. Comparison of actual outcome after repeated orthotopic liver re-transplantations (re-OLT) and the simulated outcome when second re-OLT would not have been performed

	Reality	Simulation (N = 50)		
	Current report	Stop after first re-OLT	Reallocated 30 grafts	Total
Number of patients	23	23	27	50
Total number of grafts used	76	46	30	76
Patients surviving	16 (70%)	None	20 (40%)	20
Patients deceased	7	23	7	30

grafts could have been donated to patients in need of a first graft. The overall results of primary graft transplantations are generally superior to those after repeat re-OLT, and also the costs involved are lower (5). However, from the perspective of our team, we had an existing commitment to treat these 23 patients with the help of all of our knowledge and abilities. None of the patients would have survived without repeat re-OLT. If treatment of these patients had been stopped after the first re-OLT, the currently accepted rescue modality for first graft failure, 23 patients would have died, and 30 grafts would have been saved. However, the fate of these 30 grafts that would have been used for primary transplants may not have been more favorable than the eventual outcome (see Table 4). If we make the assumption that the re-OLT rate after primary liver transplantation is 10%, as reported in the literature (3, 5–7, 21), these 30 grafts would have been used as 27 primary grafts and three first re-OLTs in 27 patients. The reported 10-yr patient survival after primary liver transplantation is 75% (3, 22, 23). Therefore, if we had reallocated these 30 grafts to 27 primary transplantations, 20 patients would have survived long term, and seven would have died. In this simulated situation, only 20 (40%) of the total of 50 patients (23 from the reported series and 27 from the group of reallocated grafts) would have survived in comparison with the 16 (70%) survivors in our series. Moreover, in the simulation, 30 patients die, because all 23 patients in our present series, and an additional seven of the patients receiving the reallocated grafts would have died. This is in contrast to the seven deaths from the reported series. This indicates that with this policy used at our institution for repeat liver transplantations, few people ultimately die than when these patients were denied their second and third re-OLTs.

It is fair to state that the difference in survival between the simulated situation (40%) and the real reported situation (70%) is an overestimation. Moreover, waiting list mortality was not taken into account in the simulated computations, because that is mathematically very difficult. However, the overestimation will approach the waiting list mortality rates reported in the literature of 10–15% (24). Subtraction of this percentage (15%) from the reported absolute survival (70%) still leaves a survival benefit for the policy described in this study.

In conclusion, we have conclusively demonstrated that with repeated re-OLTs, even up to three re-OLTs, an acceptable long-term patient survival can be obtained. This study also indicates (via a simulation calculation) that honoring the initial commitment to our patients ultimately leads to more surviving patients and fewer deaths than denying patients the possibility of re-OLT.

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Original article

Recurrence-free survival more than 10 years after liver resection for hepatocellular carcinoma

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Background: High recurrence rates after liver resection with curative intent for hepatocellular carcinoma (HCC) remain a problem. The characterization of long-term survivors without recurrence after liver resection may help improve the therapeutic strategy for HCC.

Methods: A nationwide Japanese database was used to analyse 20 811 patients with HCC who underwent liver resection with curative intent.

Results: The 10-year recurrence-free survival rate after liver resection for HCC with curative intent was 22·4 per cent. Some 281 patients were recurrence-free after more than 10 years. The HCCs measured less than 5 cm in 83·2 per cent, a single lesion was present in 91·7 per cent, and a simple nodular macroscopic appearance was found in 73·3 per cent of these patients; histologically, most HCCs showed no vascular invasion or intrahepatic metastases. Multivariable analysis revealed tumour differentiation as the strongest predictor of death from recurrent HCC within 5 years.

Conclusion: Long-term recurrence-free survival is possible after liver resection for HCC, particularly in patients with a single lesion measuring less than 5 cm with a simple nodular appearance and low tumour marker levels.

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Introduction

Hepatocellular carcinoma (HCC) is a common malignancy in Japan, and often develops in virus-infected cirrhotic liver[1]. The high incidence of recurrence following treatment renders it difficult to cure this disease completely. On the other hand, long-term survival has been reported even beyond 10 years, with or without recurrence, after potentially curative liver resection[2–4]. However, there have been few reports regarding recurrence-free survival (RFS) for more than 10 years after liver resection with curative intent for HCC[5].

The Liver Cancer Study Group of Japan (LCSGJ) has conducted a nationwide survey of patients with primary liver carcinoma since 1969 to evaluate the clinicopathological characteristics and outcomes of these patients[6]. The large-scale registration system of the LCSGJ was used here to evaluate the characteristics of patients who survived without recurrence for at least 10 years after curative liver resection. These patients were compared with patients who died from recurrent HCC within 5 years in order to gain insight into the demography and biological behaviour of HCCs. In addition, such data might be important in determining follow-up strategies, and encouraging patients to undergo treatment, including surgical resection.

Methods

A nationwide follow-up survey of all patients with primary HCC was conducted by the LCSGJ. All patients with

primary malignant liver tumours diagnosed by imaging, preoperative clinical data, and/or histopathological studies at approximately 800 institutions in Japan were registered and followed prospectively every 2 years.

At the time of this analysis, the LCSGJ database contained 142 900 patients diagnosed with a liver tumour and 130 748 patients ultimately diagnosed with HCC. The present study enrolled 20 811 patients with HCC who had undergone liver resection with curative intent before 1993, and were registered in the JCSGJ database between 1988 and 2003 (from the 10th to the 17th surveillance). The indications for hepatic resection and operative procedures were based on both anatomical location of the tumour and liver function. Follow-up ended on 31 December 2003.

Patients who survived more than 10 years without recurrence of HCC and those who died from recurrent HCC within 5 years of liver resection were identified. Patients were further examined according to the degree of background liver damage, as advocated by the JCSGJ as an alternative to the Child–Pugh score (*Table 1*)[7]. The serological presence of hepatitis B antigen was considered evidence of hepatitis B infection, and that of hepatitis C antibody as an indicator of hepatitis C infection. Hepatic resections were classified according to the terminology of the Liver Cancer Study Group of Japan[7]. The macroscopic appearance of HCC was classified into six types: type 1 (simple nodular type), type 2 (simple nodular type with extranodular growth), type 3 (confluent multinodular type), type 4 (multinodular type), type 5 (others, including infiltrative, mass and diffuse types) and unknown[6,8]. Serum levels of α-fetoprotein (AFP) and des-γ-carboxyprothrombin (DCP) were measured as tumour markers. Microscopic portal vein invasion was defined as the presence of tumour emboli within the portal vein. Intrahepatic metastasis was classified into four groups: 0 (no intrahepatic metastasis), 1 (intrahepatic metastasis to the segment in which the main tumour is located), 2 (intrahepatic metastases to two segments), 3 (intrahepatic metastases of the three or four segments). Non-cancerous liver was classified microscopically as normal, or as having chronic hepatitis, fibrosis or cirrhosis.

Hepatic recurrence of HCC was diagnosed at each centre by ultrasonography and/or dynamic computed tomography. Distant metastases were diagnosed by computed tomography (lung) and scintigraphy (bone)[9].

Table 1 Degree of liver damage according to the Liver Cancer Study Group of Japan

	Degree of liver damage		
	A	B	C
Ascites	None	Controllable	Uncontrollable
Serum bilirubin (mg/dl)	> 2·0	2·0–3·0	< 3·0
Serum albumin (g/dl)	> 3·5	3·0–3·5	< 3·0
ICG-R15 (%)	< 15	15–40	> 40
Prothrombin activity (%)	> 80	50–80	< 50

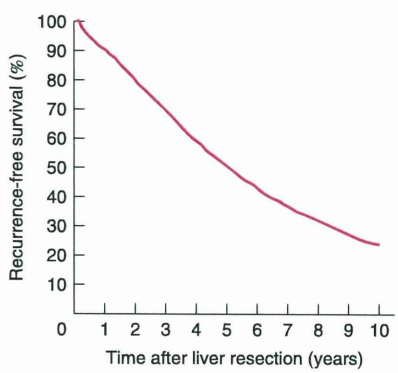
The degree of liver damage was classified as grades A, B and C based on the highest grade containing at least two of five items. Then, if two or more items scoring the same grade occur in the three grades, the higher grade is adopted as the degree of liver damage. ICG-R15, indocyanine green retention rate at 15 min.

Statistical analysis

Continuous data were expressed as mean(s.d.) and analysed by means of Student's t test. The χ^2 test was used to analyse the distribution of nominal variables, and the Wilcoxon rank sum test for analysis of ordered categorical variables. RFS curves were generated by the Kaplan–Meier method. A multivariable logistic regression model was used to investigate odds ratios. $P < 0{\cdot}050$ was considered statistically significant.

Results

Stratification according to the time of recurrence identified 281 patients who survived more than 10 years without recurrence of HCC (10-year RFS group), whereas 918 patients died from recurrent HCC within 5 years of liver resection. Median follow-up was 11·2 and 0·9 years respectively. The RFS rate at 10 years was 22·4 per cent after liver resection with curative intent (*Fig. 1*). Clinical



No. at risk	4977	3399	2253	1423	572	39
Cumulative recurrences	0	543	1047	1349	1533	1704
Cumulative deaths without recurrence	0	471	812	1110	1275	1339

Fig. 1 Recurrence-free survival after liver resection with curative intent for hepatocellular carcinoma

Table 2 Comparison of clinical data between recurrence-free survivors at 10 years and patients who died from recurrent hepatocellular carcinoma within 5 years

	10-year RFS ($n = 281$)	Died within 5 years ($n = 918$)	P§
Age (years)*	57·5(9·4)	60·8(8·5)†	< 0·001¶
Sex ratio (M : F)	219 : 62	755 : 162‡	0·115
Liver damage grade			< 0·001
A	212 (79·1)	553 (65·1)	
B	52 (19·4)	257 (30·3)	
C	4 (1·5)	39 (4·6)	
Unknown	13	69	
HBsAg-positive	82 of 255 (32·2)	179 of 812 (22·0)	< 0·001
HCV Ab-positive	103 of 198 (52·0)	356 of 474 (75·1)	< 0·001
AFP (ng/ml)			< 0·001#
< 20	140 (50·9)	272 (30·8)	
≥ 20 to < 400	73 (26·5)	345 (39·1)	
≥ 400 to < 1000	15 (5·5)	79 (9·0)	
≥ 1000	47 (17·1)	186 (21·1)	
Unknown	6	36	
DCP (mAU/ml)			< 0·001#
< 40	118 (69·4)	222 (50·5)	
≥ 40 to < 500	16 (9·4)	83 (18·9)	
≥ 500 to < 1000	36 (21·2)	135 (30·7)	
≥ 1000	0 (0)	0 (0)	
Unknown	111	478	
Operative method			0·270
> 1 segment	135 (48·2)	410 (44·9)	
Subsegment	71 (25·4)	216 (23·6)	
< 1 subsegment	74 (26·4)	288 (31·5)	
Unknown	1	4	

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). Data missing for †six and ‡one patients. RFS, recurrence-free survival; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C antibody; AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin. §χ^2 test, except ¶Student's t test and #Wilcoxon rank sum test.

Table 3 Comparison of histopathological data between recurrence-free survivors at 10 years and patients who died from recurrent hepatocellular carcinoma within 5 years

	10 year RFS ($n = 281$)	Died within 5 years ($n = 918$)	P*
Maximum tumour size (cm)			0·009
< 2	91 (32·5)	198 (21·7)	
2–5	142 (50·7)	480 (52·6)	
> 5	47 (16·8)	234 (25·7)	
Unknown	1	6	
No. of tumours			< 0·001
1	253 (91·7)	675 (74·1)	
2	20 (7·2)	145 (15·9)	
≥ 3	3 (1·1)	91 (10·0)	
Unknown	5	7	
Macroscopic type			< 0·001
1	198 (73·3)	521 (60·2)	
2	32 (11·9)	174 (20·1)	
3	28 (10·4)	69 (8·0)	
4	6 (2·2)	66 (7·6)	
5	6 (2·2)	35 (4·0)	
Unknown	11	53	
Tumour differentiation			< 0·001
Well	52 (24·0)	95 (13·7)	
Moderate	133 (61·3)	427 (61·4)	
Poor	31 (14·3)	167 (24·0)	
Unclassified	1 (0·5)	6 (0·9)	
Unknown	64	223	
Vascular invasion			0·281
Yes	4 (1·4)	23 (2·6)	
No	272 (98·6)	875 (97·4)	
Unknown	5	20	
Intrahepatic metastases			< 0·001
0	258 (92·5)	673 (75·3)	
1	15 (5·4)	154 (17·2)	
2	6 (2·2)	62 (6·9)	
3	0 (0)	5 (0·6)	
Unknown	2	24	< 0·001
Non-cancerous liver			
Normal	35 (14·4)	50 (6·6)	
Chronic hepatitis/fibrosis	105 (43·2)	189 (25·1)	
Cirrhosis	103 (42·4)	514 (68·3)	
Unknown	38	165	

Values in parentheses are percentages. RFS, recurrence-free survival. *χ^2 test.

and histopathological characteristics of the two groups are compared in *Tables 2* and *3* respectively.

In the 10-year RFS group, at the time of liver resection the background liver damage was grade A in 79·1 per cent, grade B in 19·4 per cent and grade C in 1·5 per cent. Some 32·2 per cent of these patients were positive for hepatitis B virus antigens, whereas 52·0 per cent were positive for hepatitis C virus antibody. Serum levels of AFP and DCP were normal in 50·9 and 69·4 per cent of patients respectively. Surgical procedures comprised resection of less than a subsegment in 26·4 per cent, subsegmentectomy in 25·4 per cent and resection of more than one segment in 48·2 per cent of patients.

The maximum size of HCC at resection was less than 5 cm in 83·2 per cent of patients in the 10-year RFS group. Some 91·7 per cent of these patients had a single HCC at resection. HCCs in this group were of the single nodular type in 73·3 per cent, and 61·3 per cent were moderately differentiated; most showed no vascular invasion (98·6 per cent) or intrahepatic metastases (92·5 per cent). The non-cancerous tissue was cirrhotic in 46·5 per cent.

Comparison of the characteristics of patients who survived for at least 10 years without disease recurrence and those who died from recurrent HCC within 5 years revealed significant differences in age, degree of liver damage, positivity for hepatitis B antigen and hepatitis C antibody, serum levels of AFP and serum levels of DCP

(*Table 2*). Indeed, the 10-year survivors were younger, less frequently positive for hepatitis C and more frequently positive for hepatitis B. Levels of tumour markers (AFP, DCP) were lower in this group, whereas HCCs were smaller and fewer in number. There were also statistically significant differences in macroscopic appearance, tumour differentiation, intrahepatic metastasis and non-cancerous liver histology.

Table 4 Multivariable logistic regression analysis for death from recurrent hepatocellular carcinoma within 5 years

	Odds ratio	*P*
Age (years)		
≥ 60	1·00	
< 60	1·67 (1·06, 2·61)	0·026
Maximum tumour size (cm)		
< 2	1·00	
2–5	1·10 (0·63, 1·93)	0·728
> 5	2·56 (1·16, 5·65)	0·020
No. of tumours		
1	1·00	
≥ 2	1·99 (0·85, 4·62)	0·111
Macroscopic type		
1	1·00	
2	1·44 (0·75, 2·75)	0·270
3	0·76 (0·36, 1·62)	0·473
4	1·31 (0·36, 4·78)	0·687
5	1·68 (0·50, 5·67)	0·405
Tumour differentiation		
Well	1·00	
Moderate	1·59 (0·86, 2·92)	0·138
Poor	3·33 (1·46, 7·60)	0·004
Unclassified	1·01 (0·08, 12·67)	0·995
Vascular invasion		
No	1·00	
Yes	1·21 (0·25, 5·74)	0·813
Intrahepatic metastasis		
No	1·00	
Yes	2·34 (1·02, 5·37)	0·046
Non-cancerous liver		
Normal	1·00	
Chronic hepatitis/fibrosis	0·71 (0·30, 1·72)	0·450
Cirrhosis	2·25 (0·93, 5·40)	0·071
Liver damage grade		
A	1·00	
B or C	1·58 (0·96, 2·62)	0·075
AFP (units/l)		
< 20	1·00	
≥ 20 to < 400	1·96 (1·19, 3·25)	0·009
≥ 400 to < 1000	2·88 (1·19, 6·94)	0·019
≥ 1000	1·63 (0·86, 3·08)	0·134
DCP (units/l)		
< 40	1·00	
≥ 40 to < 500	2·73 (1·28, 5·41)	0·004
≥ 500 to < 1000	0·90 (0·39, 2·08)	0·804
≥ 1000	1·42 (0·76, 2·68)	0·273

Values in parentheses are 95 per cent confidence intervals. AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin.

Multivariable analysis revealed that tumour differentiation had the highest odds ratio related to death from recurrent HCC within 5 years, followed by raised levels of AFP and DCP (*Table 4*). When both the size and number of HCCs were categorized, the frequency of single HCC was significantly higher for any diameter of HCC in the 10-year RFS group than in patients who died from recurrent HCC within 5 years (data not shown).

Among patients whose levels of AFP (400–1000 units/l) and DCP (500–1000 units/l) were moderately raised, those with a single HCC had a lower risk of death from recurrent HCC than those with multiple tumours (data not shown). The number of HCCs yielded a higher odds ratio than the diameter of HCC in this specific group.

Discussion

The present study characterized tumour and patient factors among patients who survived without recurrence for 10 years after liver resection with curative intent for HCC. Although the characteristics of 10-year survivors after liver resection have already been investigated, there are few reports on 10-year RFS[2–5,10]. The present research was conducted as a nationwide large-scale comprehensive study of long-term recurrence-free survivors of HCC following liver resection in Japan.

In the present study, patients in the 10-year RFS group were younger with less background liver damage than patients who died from recurrent HCC within 5 years after liver resection. This was probably because there was less inflammatory change resulting from hepatitis C infection in the 10-year RFS group. The importance of underlying liver disease has been noted previously with regard to the degree of liver fibrosis and cirrhosis[10]. Underlying liver disease has more impact on patient survival than tumour factors[11]. Although two extreme HCC groups were compared in the present study (long-term RFS and short-term relapse), the present findings are of importance in determining possible factors associated with long-term RFS after curative liver resection.

Failure to detect latent intrahepatic HCC before surgery has no prognostic impact on the outcome or recurrence of HCC after liver transplantation[12,13]. The explanted diseased liver may show early HCCs that could not be detected before surgery, which can therefore appear as multicentric HCC on later examination. In the present study, patients in the 10-year RFS group had better liver function, despite a higher rate of positivity for hepatitis B surface antigen. Although the inflammatory activity in the resected liver was not investigated here, it was likely to have been lower in the remnant liver of the long-term survivors.

Tumour markers such as AFP or DCP have been reported to predict the early recurrence of HCC, even in the absence of microvascular invasion in the resected specimen[14,15]. The documentation of microvascular invasion depends on the slice width of the resected specimen and the number of slices investigated. Therefore, early recurrence can occur despite the absence of documented microvascular invasion. However, AFP or DCP levels are raised in nearly 60 per cent of patients with HCC, reflecting the biological behaviour of malignant tumours. The present data indicate that patients with no increase in AFP and DCP levels before surgery have a higher chance of survival without recurrence. In multivariable analysis, both tumour markers were independently associated with death due to recurrence after liver resection with curative intent. Furthermore, patients with a single HCC who had moderately raised AFP and DCP levels still had the prospect of surviving for longer after liver resection than those with high levels of tumour markers.

Considering the number and size of HCCs, a considerable percentage of patients in the 10-year RFS group had a single HCC (91·7 per cent) at the time of liver resection. Even with a raised AFP or DPC level, the risk of early death from recurrent HCC increased when there was more than one lesion. In other words, if a single HCC is found, a patient has an increased chance of surviving for longer after liver resection with curative intent.

Macroscopic HCC appearance was valuable for predicting 10-year RFS after curative liver resection, as shown previously[8]. HCCs of a contiguous multinodular type with clustering of small and contiguous nodules, and simple nodular types with extranodular growth carry a worse prognosis, most likely owing to microvascular invasion. In line with this, patients with these macroscopic types of HCC had a lower chance of long-term survival after liver resection in the present series.

The authors' group previously reported that anatomical resection has therapeutic value for treating patients with HCCs of 2–5 cm in diameter[16]. However, in the present study, this benefit of curative resection was not confirmed, even for HCCs with a diameter of 2–5 cm. This may have been because two extreme patient groups were compared. For example, even for HCC of 2–5 cm in size, the macroscopic appearance, vascular invasion, inflammatory status and fibrosis in the tumour-bearing liver may have been largely different between the two groups.

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Clinical Science

Perioperative synbiotic treatment to prevent infectious complications in patients after elective living donor liver transplantation: a prospective randomized study

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KEYWORDS:
Synbiotic therapy;
Living donor liver transplantation;
Infectious complication

Abstract

BACKGROUND: Although the effect of synbiotic therapy using prebiotics and probiotics has been reported in hepatobiliary surgery, there are no reports of the effect on elective living-donor liver transplantation (LDLT).

METHODS: Fifty adult patients undergoing LDLT between September 2005 and June 2009 were randomized into a group receiving 2 days of preoperative and 2 weeks of postoperative synbiotic therapy (*Bifidobacterium breve*, *Lactobacillus casei*, and galactooligosaccharides [the BLO group]) and a group without synbiotic therapy (the control group). Postoperative infectious complications were recorded as well as fecal microflora before and after LDLT in each group.

RESULTS: Only 1 systemic infection occurred in the BLO group (4%), whereas the control group showed 6 infectious complications (24%), with 3 cases of sepsis and 3 urinary tract infections with *Enterococcus* spp ($P = .033$ vs BLO group). No other type of complication showed any difference between the groups.

CONCLUSIONS: Infectious complications after elective LDLT significantly decreased with the perioperative administration of synbiotic therapy.

The bowel has bacterial flora, in which 100 billion bacteria are present with a weight of 1 kg.[1] Bacterial translocation can occur if the intact environment is compromised, leading to the provocation of several cytokine networks and multiple organ failure in the end.[2–5] Liver transplant recipients in particular usually have a long history of liver disease and suffer portal hypertension, which leads to malnutrition.[6] Therefore, the mucosa of their bowels could be atrophic and more susceptible to bacterial translocation, which leads to endotoxemia and multiple organ failure.[7–9]

"Synbiotic therapy" is the medical term for comprehensive prebiotic therapy combined with probiotic therapy.[10] It has been used for the amelioration of stool character, the suppression of toxic substances, and immunomodulation for various infectious diseases and is reported to provide good therapeutic efficacy.[9–11] Probiotics are bacteria that can provide beneficial effects by maintaining the balance of resident bacteria in the bowel, such as bifidobacteria and lactobacteria.[12,13] Generally, probiotics increase the intestinal motility and stabilize the intestinal barrier for bacterial location.[14,15] Furthermore, probiotics, which are living bac-

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Table 1 Patient characteristics

Variable	BLO group (n = 25)	Control group (n = 25)	*P*
Age (y)	56 (33–66)	57 (25–68)	NS
Men/women	13/12	16/9	NS
Primary disease	LC-C (n = 9)	LC-C (n = 13)	NS
	LC-B (n = 5)	LC-B (n = 7)	
	LC-Al (n = 3)	Caroli disease (n = 1)	
	LC-AIH (n = 2)	FHF (n = 1)	
	PSC (n = 3)	LC-Al (n = 1)	
	PBC (n = 2)	PV thrombus (n = 1)	
	LC unknown (n = 1)	PSC (n = 1)	
ABO incompatibility	9 (36%)	4 (16%)	NS
GV/SLV ratio (%)	39 (24.8–61)	41.5 (23.6–57)	NS
MELD score	15 (2–34)	16 (4–41)	NS
Concomitant HCC	12	12	NS

Data are expressed as median (range) or as number (percentage).

BLO = *Bifidobacterium breve, Lactobacillus casei,* and galactooligosaccharides; FHF = fulminant hepatic failure; GV = graft volume; HCC = hepatocellular carcinoma; LC-AIH = liver cirrhosis due to autoimmune hepatitis; LC-Al = liver cirrhosis due to alcohol intoxication; LC-B = liver cirrhosis due to hepatitis B virus; LC-C = liver cirrhosis due to hepatitis C virus; LC unknown = liver cirrhosis of unknown origin; MELD = Model for End-Stage Liver Disease; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis; PV = portal vein; SLV = standard liver volume.

teria, can protect the innate immune system with cytokine modulation. By contrast, prebiotics are an ingredient made from food and delivered to the large bowel, which can stimulate the proliferation of beneficial bacteria such as bifidobacteria. Prebiotics can reach the colon without any transformation and serve as nutrition for probiotics.[2] Synbiotic therapy reduces the rate of infection after pylorus-preserving pancreaticoduodenectomy,[16] major hepatectomy for bile duct cancer,[17] deceased-donor whole-liver transplantation,[18,19] and acute pancreatitis.[20] However, no reports have indicated whether infectious complication can be reduced by synbiotic therapy after living-donor liver transplantation (LDLT). Because LDLT is always partial transplantation, postoperative portal hypertension is higher in LDLT compared with whole-liver transplantation.[21]

Therefore, this prospective randomized controlled study was conducted to determine if synbiotic therapy during the perioperative period is effective in reducing infectious complications for recipients undergoing LDLT.

Methods

Patients

This prospective study was approved by the local institutional review board at Nagasaki University Hospital, and written informed consent was obtained from all patients.

Fifty liver transplant recipients at Nagasaki University Hospital treated between June 2005 and June 2009 were enrolled in this study. The α error was set at 5%, with power of 80%. According to previous reports, infectious complications occur in 40% of liver transplant recipients and could be reduced by synbiotic therapy to 10%.[18,19] Therefore, the calculated sample size was 25 patients for each group.

Patients were randomly assigned to groups receiving (n = 25) or not receiving (n = 25) synbiotic therapy. The characteristics of the patients are shown in Table 1. The primary endpoint of this study was to the reduction of infectious complications after LDLT with synbiotic therapy.

Liver transplantation

All partial liver grafts were preserved in University of Wisconsin solution and implanted using a piggyback technique, as previously described.[22] Surgeons experienced in microscopic surgery anastomosed all the hepatic arteries with the aid of a surgical microscope. Graft selection was based on the results of a volumetric study using computed tomography to obtain a ratio of graft volume to standard liver volume of >35% in the recipients. All patients received intravenous prophylaxis with amoxicillin and cefotiam for 4 days as a standard protocol. Empiric therapy was initiated in the event of infection, and subsequently antibiotics were narrowed on the basis of the resistance index.

A dual or triple immunosuppressive regimen was used, which included tacrolimus or cyclosporine A, prednisolone, and/or mycophenolate mofetil. Patients with compromised renal function were administered induction therapy with interleukin-2 antibodies. Only biopsy-proven rejections were treated if clinical and laboratory signs mandated steroid bolus treatment. Rituximab (anti-CD20 antibody) was used preoperatively for immunosuppression in ABO-incompatible patients.

Age, gender, primary liver disease, ABO incompatibility, median graft volume versus standard liver volume, Model for End-Stage Liver Disease score at time of LDLT,

and concomitant hepatocellular carcinoma were compared between the group receiving synbiotic therapy and the control group.

Subsequently, at 24 hours after LDLT, all patients received enteral nutrition with Elental (Ajinomoto Pharmaceutical Ltd, Tokyo, Japan), which is an elemental diet, through a tube jejunostomy made during liver transplantation. The initial infusion rate at 1 kcal/mL was 20 mL/h, and if tolerated the rate was increased 60 mL/h until sufficient oral intake was possible. The composition of Elental has been described elsewhere.[23]

Synbiotic therapy

All patients had started the oral administration of Yakult BL antiflatulent (Yakult Honsha, Tokyo, Japan), containing 20 mg of living *Lactobacillus casei* strain Shirota, 15 mg of living *Bifidobacterium breve* strain Yakult, and galactooligosaccharides 15 g/d (Oligomate 55; Yakult Honsha) 3 times per day from 2 days before elective LDLT, continued for 2 weeks after LDLT via either a tube jejunostomy or orally. Usually, both prebiotics and probiotics were taken with 10 mL of tap water. We selected this formula of synbiotics on the basis of a previous report on major hepatectomy.[16]

The rates of infectious complications and patient survival were recorded, and stool cultures were also performed.

Statistical analysis

All data are expressed as median values with ranges. Statistical analysis was performed using the Mann-Whitney U test for continuous values and the χ^2 test for categorical values. A statistically significant difference was defined as a P value $< .05$. StatView version 5.0 (Abacus Concepts, Berkeley, CA) was used for all statistical analyses.

Results

All patients tolerated synbiotic therapy throughout the study period. There was no difference in the patient characteristics between the groups (Table 1). Figure 1 shows the result of cultured bacteria in the feces. Generally, *Escherichia* spp, *Enterobacter* spp, and *Klebsiella* spp were regarded as normal bacterial flora in the stool. There was no significant pattern of the change of bacterial species between the groups. However after LDLT under immunosuppression, *Enterococcus* spp became evident in both groups in about 25% of the patients.

Table 2 that infectious complication occurred after LDLT in 6 of 25 of the patients in the control group (24%) and in 1 of 25 (4%) in group receiving synbiotic therapy ($P < .05$). In particular, the rate of urinary infection was higher without synbiotic therapy. The rate of intra-abdominal infection was not statistically different. *Enterococcus* spp and methicillin-resistant *Staphylococcus aureus* were the main bacteria related to the infection. The postoperative date of infection varied. Some infectious complication occurred after the termination of synbiotic therapy.

Table 3 shows that there was no significant difference between the groups in other complications after LDLT. In addition, there were no differences in the intensive care unit period, hospitalized period, and mortality rate between the groups.

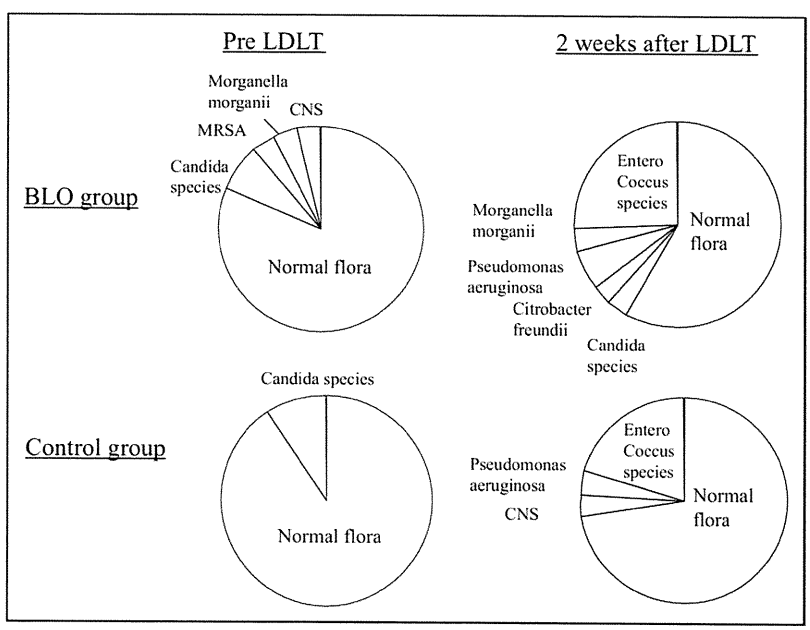

Figure 1 Bacterial profile in fecal culture. Cultured bacteria in the feces of the patients undergoing LDLT in each group. BLO = *Bifidobacterium breve*, *Lactobacillus casei*, and galactooligosaccharides; CNS = coagulase-negative staphylococci; MRSA = methicillin resistant *Staphylococcus aureus*.

Table 2 Infectious complications after LDLT

Variable	BLO group (n = 25)	Control group (n = 25)	*P*
Type of infection	1 catheter infection (POD 19)	3 sepsis (PODs 11, 10, and 9) 3 urinary tract infections (PODs 7, 8, and 5)	<.05
Bacteria cultured in blood	1 *Enterobacter asburiae* (POD 19)	2 MRSA (PODs 10 and 9) 1 MRSA + *Candida glabrata* (POD 11) 3 *Enterococcus faecium* (PODs 7, 8, and 5)	
Intra-abdominal infection	1 (4%) *Klebsiella oxytoca* + *Enterococcus faecium* (POD 19)	2 (8%) 1 *Enterobactor asburiae* (POD 19) 1 *Enterococcus faecium* (POD 14)	NS

BLO = *Bifidobacterium breve, Lactobacillus casei,* and galactooligosaccharides; MRSA = methicillin resistant *Staphylococcus aureus;* POD = postoperative day.

Comments

This prospective randomized study demonstrated that synbiotic therapy successfully reduced the rate of infectious complications after LDLT, which has a greater chance to induce temporary portal hypertension leading to bacterial translocation. The portal venous pressure after LDLT should have been elevated in the current series of patients, because the graft volume versus standard liver volume ratio was about 40%.[21] Therefore, synbiotic therapy may be potentially more effective in patients after LDLT than deceased-donor liver transplantation. In addition, LDLT is partial transplantation, in which liver regeneration should occur to support the patient's life. Infection itself was reported to reduce the magnitude of liver regeneration, so synbiotic therapy should be used for the patients undergoing LDLT.[24]

The patients in the present study received enteral nutrition, which has been shown to reduce the rate of infection from 29% to 14%.[25,26] This is probably why the rate of infection in this study was lower than in previous reports with synbiotic therapy. In addition, the rate of acute cellular rejection was not changed by synbiotic therapy. In a previous study, the rate of acute cellular rejection was reduced from 44% to 7% by enteral nutrition after whole-liver transplantation.[27] There was no difference in the rejection rate, even though there were more ABO-incompatible LDLT patients in the synbiotic group than in the control group.

Methicillin-resistant *S aureus* and *Enterococcus* spp were the principle bacteria causing sepsis, although gram-negative gut-derived bacteria are thought to be found in septic patients. Although there was no explanation for the gram-positive bacteria in this series, *Enterococcus* spp were frequently observed as the dominant bacteria after LDLT in the feces.[28] Immunosuppression and the duration of our antibiotic use might have cause *Enterococcus* sepsis in partial liver transplant recipients. In addition, the reduction of urinary tract infections was reported in a previous study, consistent with the current data, indicating that synbiotic therapy is likely to be responsible for the reduction of urinary tract infection.[29] Previous authors have speculated that in addition to their impact on bacterial translocation, probiotics act via several other mechanisms. For instance, they can reduce and eliminate potentially pathogenic microorganisms, reduce and eliminate various toxins and mutagens from the urine and feces, modulate innate and adaptive immune defense mechanisms, promote apoptosis, and release numerous nutrients, antioxidants, and growth factors from consumed fibers. These functions might all be important for the reduction of infections in surgical patients. However, a definite mechanism regarding the reduction of urinary tract infection awaits further investigation.[3,25,29,30]

In conclusion, infectious complications after LDLT were significantly decreased with synbiotic therapy. It is possible to achieve ecologic liver transplantation using synbiotic therapy while maintaining an intact environment in the body.

Table 3 Other complications

Variable	BLO (n = 25)	Control (n = 25)	*P*
Others	2 ACR 3 CMV 1 HAT 1 HPS 1 TMA 1 adrenal insufficiency	3 ACR 3 CMV 1 HAT 1 HPS 1 NOMI	NS
ICU period (days)	7 (4–35)	7 (2–48)	NS
Hospitalized period (days)	40 (16–132)	33 (16–97)	NS
Mortality	3	3	NS

Data are expressed as median (range) or as numbers.

ACR = acute cellular rejection; BLO = *Bifidobacterium breve, Lactobacillus casei,* and galactooligosaccharides; CMV = cytomegalovirus; HAT = hepatic arterial thrombus; HPS = hemophagocytic syndrome; ICU = intensive care unit; NOMI = nonocclusive mesenteric ischemia; TMA = thrombolytic microangiopathy.

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SURGERY TODAY

Review Article

Liver Transplantation for Patients with Human Immunodeficiency Virus and Hepatitis C Virus Coinfection with Special Reference to Hemophiliac Recipients in Japan

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Abstract
Liver transplantation for patients with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) remains challenging. The advent of highly active antiretroviral therapy (HAART) for HIV has reduced mortality from opportunistic infection related to acquired immunodeficiency syndrome dramatically, while about 50% of patients die of end-stage liver cirrhosis resulting from HCV. In Japan, liver cirrhosis frequently develops after HCV–HIV coinfection resulting from previously transfused infected blood products for hemophilia. The problems of liver transplantation for those patients arise from the need to control calcineurin inhibitor with HAART drugs, the difficulty of using interferon after liver transplantation with HAART, and the need to control intraoperative coagulopathy associated with hemophilia. We review published reports of liver transplantation for these patients in the updated world literature.

Key words Liver transplantation · Hepatitis C virus · Human immunodeficiency virus · Coinfection · Highly active antiretroviral therapy

Introduction

According to a report compiled by the Japanese Ministry of Health, Labour and Welfare in October 2006, the number of HIV-infected patients in Japan was 8071 (6275 males and 1796 females), and this number has increased further since.[1] In 2008 there were 1557 new cases reported, including 1126 HIV-positive cases and 431 acquired immunodeficiency syndrome (AIDS) cases.[2] The possible routes of infection include sexual contact, through contaminated or unheated blood products, and mother-to-child transmission. When HIV infection is contracted through blood products, there is often coinfection with HCV.

Since 1995, there has been a major change in the cause of death of HIV-infected patients. It is believed that the major factor contributing to these trends is the improved HIV control achieved in recent years with highly active antiretroviral therapy (HAART).[3] HAART is defined as a combination of drugs from different classes of HIV therapy, comprising nucleoside reverse transcriptase inhibitors (NRTIs), and either non-nucleoside reverse transcriptase inhibitors (NNRTIs) or a protease inhibitor (PI). If the compliance is 95% or more, this therapy is successful in more than 50% of patients.[3–5]

This review focuses on liver transplantation in Japanese patients with HIV and HCV, especially those in whom the disease was caused by receiving contaminated blood products in the past and who may be candidates for liver transplantation.

Epidemiology of HIV–HCV Coinfection in Patients with Hemophilia in Japan

According to a survey by the Ministry of Health, Labour and Welfare in the 2008 fiscal year in Japan, 602 patients with hemophilia A (factor 8 deficiency) and 183 with hemophilia B (factor 9 deficiency) were alive with HIV infection (Table 1).[6] Among these, 524 with hemophilia A (87%) and 162 with hemophilia B (89%) also had HCV infections and liver disease (Table 2). Of the 524 persons with hemophilia A, 33 (6.3%) had cirrhosis, 5 (0.9%) had liver cancer, and 2 (0.4%) had liver failure. Two of these patients underwent a liver transplant procedure. It is highly possible that about 50 of the patients

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Table 1. Coagulation disorders in Japan

	Hemophilia				
	A	B	VWD	VWD-related disease	Total
Total	4211	916	892	452	6471
Male	4185	908	406	246	5745
Female	29	8	486	206	726
HIV negative					
Total	3609	733	885	448	5675
Male	3583	725	404	245	4957
Female	26	8	481	203	718
HIV positive					
Total	602	183	7	4	796
Male	602	183	2	1	788
Female	0	0	5	3	8

Source: Official Report of the National Surveillance on Coagulation Disorders in Japan, 2008
HIV, human immunodeficiency virus; VWD, von Willebrand disease

Table 2. Stage of liver disease in patients with hemophilia and HIV infection (only reported surviving cases with HCV coinfection)

	No hepatitis	Acute hepatitis	Chronic hepatitis	Liver cirrhosis	HCC	Liver failure	Cured with IFN	Spontaneous cure	LT	Total
Hemophilia A	45	2	350	33	5	2	59	26	2	524
Hemophilia B	15	1	100	11	6	0	19	8	2	162
Total	60	3	450	44	11	2	78	34	4	686

Source: Official Report of the National Surveillance on Coagulation Disorders in Japan, 2008
HIV, human immunodeficiency virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LT, liver transplantation; IFN, interferon

with cirrhosis may be candidates for liver transplantation in the future. In fact, this survey revealed that one-third of the deaths of HIV–HCV coinfected patients with blood-borne diseases were caused by liver disease.

A characteristic that should be taken into account when using imported blood products is that the proportion of patients with HCV genotype 1b is low, at 25% vs 70% in general for Japanese, and the proportion of patients with HCV genotype 3a is high, at 23%. Also, one study found that the proportion of patients with HIV–HCV coinfection with an HCV titer below the level of sensitivity of the assay was significantly lower than the proportion of such patients among non-HIV cases of HCV infection, at 44.0% vs 55.4%, respectively.[7] There have been a few reports from other countries on the problems associated with HCV and HIV infections in hemophiliac patients.[8,9]

Liver Transplantations in HIV–HCV Coinfected Patients

Indications for Liver Transplantation in Patients with HIV–HCV Coinfection

Regardless of the presence of hemophilia, the indications for and methods of liver transplantation are the same for patients with HIV–HCV coinfection. Therefore, information on liver transplantation for HIV–HCV coinfected patients without hemophilia is presented in this section. In fact, after successful liver transplantation, hemophilia can normally be cured. In principle, as for a non-HIV-infected patient, liver transplantation is indicated for patients with type C cirrhosis in liver failure and no expectation of a long-term prognosis.[10–14] Liver transplantation is also indicated for patients not yet in liver failure, but with severe liver damage caused by HAART, especially those with chronic hepatitis C, who need to suspend or stop HAART.[15–18] For patients receiving HAART, the indication needs to be considered in terms of both hepatic reserve and status of the HIV infection. Liver transplantation may also be indicated for hepatocellular carcinoma that develops during follow-up.[19] The conditions for liver transplantation are often defined as follows: AIDS symptoms have not surfaced; the CD4+ lymphocyte count is 200–250/μl or above; and as a result of HAART, the amount of HIV in the blood is below the level of sensitivity of the assay. However, there are cases of pancytopenia resulting from portal hypertension and, as such, some institutions believe that the criterion for liver transplantation resolved be a CD4+ lymphocyte count of 100/μl or more.[19–22] Therefore, an issue to be resolved is whether

the indication can be based solely on a CD4+ lymphocyte count. Although a ratio of CD4 to CD8 lymphocyte count of 14% or greater is also considered an indication, individual institutions still refer to their own criteria. A recent study found a significant correlation between the preoperative model for end-stage liver disease (MELD) score and the postoperative survival rates of HIV–HCV coinfected patients: this also warrants investigation.[23]

Results of Liver Transplantation for Patients with HIV–HCV Coinfection

Liver transplantation from deceased donors has been performed in HIV patients since the 1980s in the United States and Europe. Initially the results were poor, with survival rates of only about 47%,[24] but this has improved remarkably since the introduction of HAART (Table 3). According to a review article published in 2004, 51 HIV-positive patients received liver transplantation between 1996 and 2004 worldwide, with liver damage caused by HCV being the indication in 68%. Since 1997, liver transplantation has been performed in 29 HIV patients at the University of Pittsburgh: 26% of these patients were hemophiliac and 89% were HCV-positive.[25] According to a retrospective study by the United Network for Organ Sharing, involving 138 HIV-positive persons and 30520 HIV-negative persons and evaluating liver transplantation, from 1997 when HAART was introduced and thereafter, the prognosis of patients who were only HIV-positive was relatively good.[26] In this study, the prognosis of HIV–HCV coinfected patients was worse than that of patients who were positive only for HIV. A series of reports are listed in Table 3.[13,20,21,25–34] In reality, in addition to those listed there have been many sporadic reports, such as reviews, regarding expectations for liver transplantation, and assessments of indications.

A recent important study in France, on 14 patients, provided details on interferons, HAART therapy, and liver fibrosis.[33] In all patients, the preoperative amount of HIV in the blood was below the level of sensitivity, and the CD4+ T-cell counts ranged from 85 to 1015. As for calcineurin inhibitors, tacrolimus 0.5 mg per week was started in the 2nd week after surgery in principle; however, there were five cases (36%) of an overdose. HAART was recommenced in the 2nd week after surgery, resulting in the long-term administration of steroids. Liver biopsies in the 12th month after liver transplantation revealed one case of fibrosing cholestatic hepatitis (FCH), one case of fibrosis stage F3, two cases of F2, and five cases of F1. The prognosis after transplantation was thought to be encouraging, since there was only one death as a result of FCH in the series.

Living Donor Liver Transplantation for Patients with HIV–HCV Coinfection

The Koike Group of the Ministry of Health, Labour, and Welfare reported seven cases of living donor liver transplantation (LDLT) for HIV–HCV coinfected patients with hemophilia at The University of Tokyo, and one at Hiroshima University.[35,36] The HCV genotypes were 1a and 1b ($n = 1$), 1b and 3a ($n = 1$), 2a ($n = 1$), 2a and 2b ($n = 1$), and 3a and 1b ($n = 1$). The HVC-RNA levels ranged from 2.8 to 1410 kIU/ml, the HIV-RNA levels in two cases were 50 copies/ml or less, being below the sensitivity level, and the CD4+ T-cell counts ranged from 120 to 618/μl and were 250/μl or less in two cases. At the time of the report in 2005, four patients were alive. Small bowel bleeding (suspected cytomegalovirus enteritis) and graft dysfunction were cited as the causes of death of the nonsurviving patients. Interestingly, interferon therapy was given after surgery to the surviving patients, whereas it was suspended in the two patients who died. HAART therapy was not given to one patient on the grounds that the HIV virus disappeared as the interferon treatment progressed. The report stated that the administration of factor 8 products was never required after surgery for patient #1.

Living donor liver transplantation from a hemophilia carrier was reported in 2002,[37] and it seems that LDLT has been performed in up to 10 patients in Japan. As noted in the section on epidemiology, there are some 50 patients coinfected with HIV–HCV from blood products, in whom liver failure has developed. They, like other patients with chronic hepatitis, may be candidates for liver transplantation, so it is necessary to collect sufficient information.

Problems with Liver Transplantation in HIV–HCV Coinfected Patients with Hemophilia

The Blood Concentration of the Calcineurin Inhibitor Used in Combination with HAART Is Increased

The risk of opportunistic infections caused by a delay in starting HAART and the appropriate time to start HAART has not been established. Moreover, early initiation of the therapy is associated with a high risk of drug-induced liver damage.[38,39] A new drug, Ralteglavir, does not interfere with the metabolism of the calcineurin inhibitor, and might reduce the chance of overshooting the trough level of the calcineurin inhibitor.[40]

Progression of HCV Recurrence Is Accelerated in These Patients Compared with Those Who Are Only HIV-Positive[41]

The HIV virus population dynamics manifest via the immune systems, which are targeted by antiviral drugs such as interferon and ribavirin as well as the HAART