the recipient required the graft, the hilar plate, including the hepatic duct, was precisely divided with scissors, and the stump of the remnant bile duct was closed with continuous, 6-0 absorbable monofilament sutures (PDS II, Ethicon, Somerville, NJ). Cholangiography with C-arm fluoroscopy was then performed once again in order to check for biliary leakage and strictures in the remnant bile duct (Fig. 2d). The liver graft was then removed after the hepatic artery, portal vein, and hepatic vein were divided.

Biliary reconstruction in recipients

Biliary reconstruction in the recipients was performed by Roux-en-Y hepaticojejunostomy or duct-to-duct anastomosis, with or without biliary stenting, and with interrupted, 6-0 absorbable monofilament sutures (PDS II, Ethicon, Somerville, NJ) (Table 1). Duct-to-duct anastomosis was the first line, and hepaticojejunostomy was performed only in cases of biliary atresia and primary sclerosing cholangitis, and in cases in which the quality of the recipient bile duct was not good for various reasons, such as biliary ischemia. In case of multiple bile ducts in the graft, duct plasty was performed whenever possible [4], and duct-to-duct anastomosis was still the first line for biliary reconstruction. Concerning decreasing the incidence of biliary atresia, the incidence of hepaticojejunostomy was significantly lower in group B (Table 1).

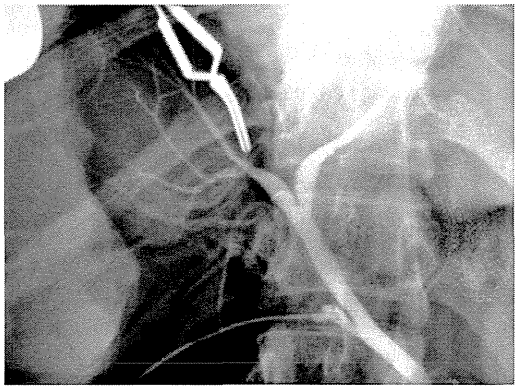

Fig. 1 Our original procedure for bile duct division. The bile duct is divided under ordinary cholangiography by placing a small vascular clip around the hepatic duct

Results

Incidence of multiple bile ducts in grafts

The characteristics of the biliary anatomy increase the probability of multiple bile ducts in right lobe grafts over that in left lobe grafts [5]. The incidence of multiple ducts in right lobe grafts was compared between groups. In the procurement of 51 right lobe grafts, the incidence of multiple bile ducts was significantly reduced by the current procedure [20/28 (71%) in group A vs. 7/23 (30%) in group B, $P < 0.01$, Fisher's test]. In these cases, anatomic variation was similar in both groups, i.e., according to the classification system of Varotti et al. [5] (Fig. 3): type 1 [right anterior and right posterior hepatic ducts (HD) join together to form the right HD: 19/28 (67.9%) in group A

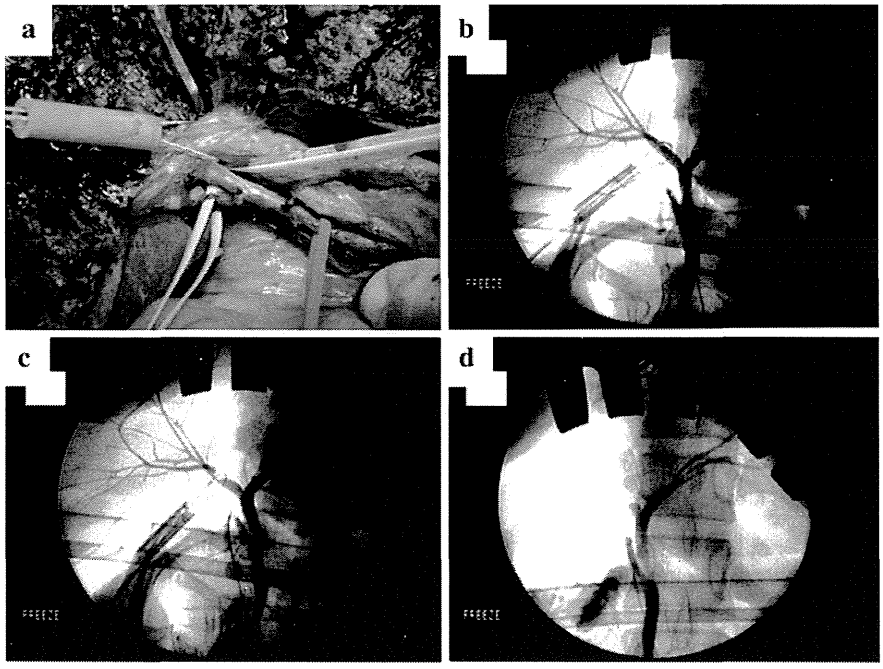

Fig. 2 Bile duct division in the procurement of a right lobe graft. The right hilar plate is encircled with a radiopaque marker filament, and sufficient surrounding tissue is preserved without exposure of the bile duct (**a**). C-arm cholangiography revealed that the radiopaque marker filament was placed at an adequate point at the right hepatic duct (**b**). The radiopaque marker filament was pulled in order to verify the cutting point (**c**). C-arm cholangiography after bile duct division revealed that the bile duct was cut at the optimal point, without inducing a stricture in the remnant left hepatic duct (**d**)

vs. 17/23 (73.9%) in group B]; type 2 [the right HD is absent and the right anterior HD and right posterior HD join directly to the confluence with the left HD to form the common HD: 2/28 (7.1%) in group A vs. 3/23 (13.0%) in group B]; type 3 [the right anterior HD or the right posterior HD open directly into the left HD: 6/28 (21.4%) in group A vs. 3/23 (13.0%) in group B]; type 4 [the right anterior HD or the right posterior HD open directly into the common HD: 1/28 (3.6%) in group A vs. 0/23 (0%) in group B)].

Bile duct division in complex cases

In cases involving multiple bile ducts in the graft, one hilar plate was encircled, including all of the hepatic ducts (Fig. 4). In these cases as well, the use of a radiopaque marker filament as the reference for the optimal cutting point was feasible and allowed preservation of the surrounding tissue. In cases involving a right posterior segment graft, it can generally be relatively difficult to determine the optimal cutting point, because the targeted point tends to be more distal and supports smaller bile duct(s); however, in all of our five donor cases involving this type of graft, we easily identified the optimal cutting point without any difficulty (Fig. 5). In some cases involving a complex variation in the bile duct branching pattern (i.e., right posterior hepatic duct independently branching from the left hepatic duct), we were able to avoid bile duct injury in the donor by clearly making the cutting point with pulling the radiopaque marker filament (Fig. 6).

Biliary complications in donors

A total of 16 complications (18.4%) were seen in the donors (6 bile leakages, 3 wound infections, 2 pleural effusions, 2 cases of gastric stasis, 1 portal vein thrombosis, 1 case of postoperative bleeding, and 1 paralytic ileus). All

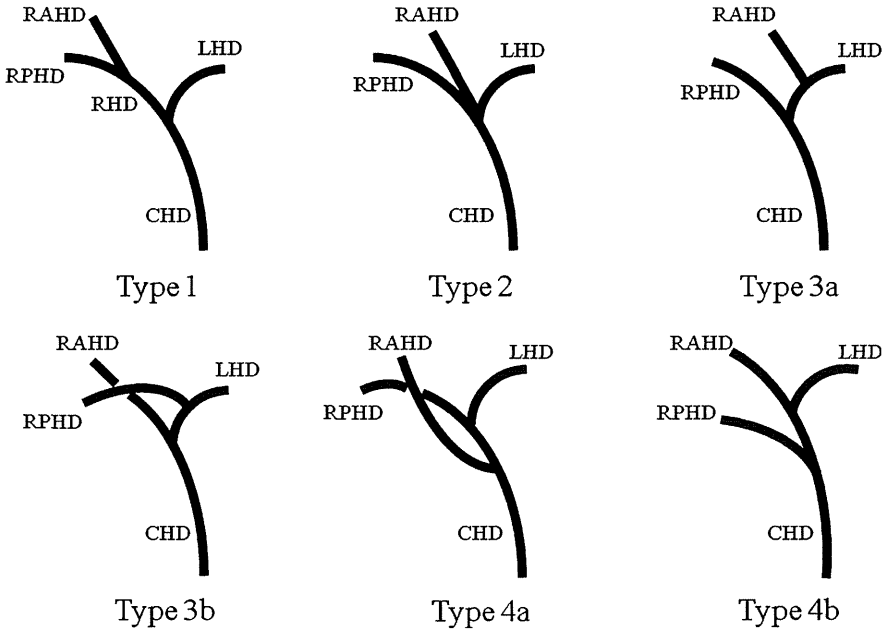

Fig. 3 Classification of the biliary tree anatomy by Varotti et al. [5]. *CHD* common hepatic duct, *LHD* left hepatic duct, *RAHD* right anterior hepatic duct, *RPHD* right posterior hepatic duct

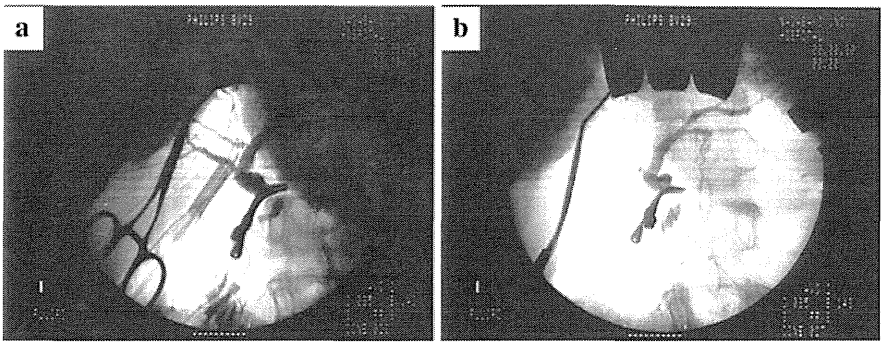

Fig. 4 Bile duct division in the procurement of a right-lobe graft with multiple ducts. The right hilar plate, including both the right anterior branch and the right posterior branch, is encircled by a radiopaque marker filament (**a**). There was no stricture in the remnant left hepatic duct after division (**b**)

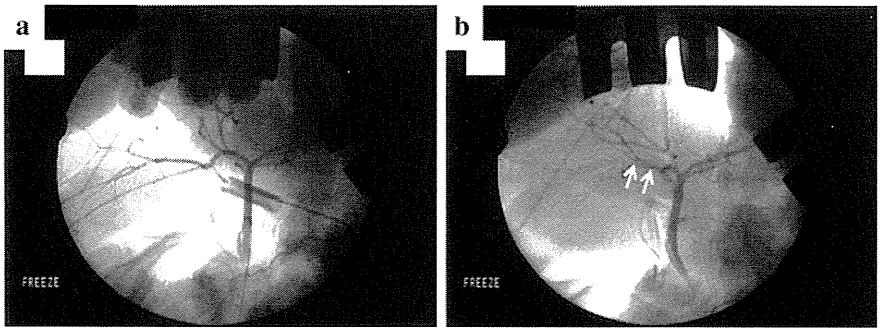

Fig. 5 Bile duct division in the procurement of a right posterior segment graft. A radiopaque marker filament was placed at an adequate point in the right posterior hepatic duct (**a**). After division of the right posterior hepatic duct, there was no stricture in the remnant right anterior hepatic duct (*arrows*, **b**)

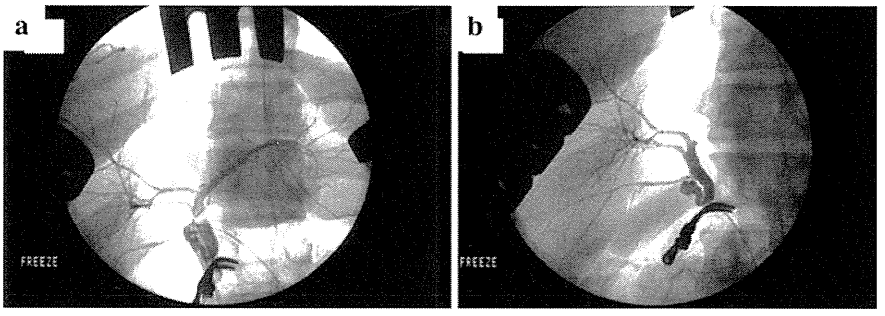

Fig. 6 Bile duct division in the procurement of a left lobe graft, in which the right anterior hepatic duct branched from the left hepatic duct (**a**). The bile duct was divided at an adequate point without subsequent stricture in the remnant right anterior hepatic duct (**b**)

bile leakage cases were treated by percutaneous drainage, and all spontaneously resolved without requiring surgical intervention. There was no significant difference in the incidence of bile leakage between the groups [4/37 (10.8%) in group A vs. 2/50 (4.0%) in group B]. No biliary strictures were observed in any of the donors in either of the groups. All donors are alive and currently doing well, carrying out normal daily activities after a median follow-up period of 43 months (range 8–136).

Biliary complications in recipients

The incidence of biliary stricture requiring endoscopic or surgical treatment of recipients was compared between adult cases in both groups (>18 years). It would not be appropriate to formally compare the incidence of biliary complications in recipients according to the groups as defined here, because the follow-up period for group B was significantly shorter than that for group A. However, it should be noted that the incidence of biliary stricture was non-significantly lower in group B than group A [i.e., 9/37 (24.3%) in group A vs. 8/50 (16.0%) in group B].

Discussion

Biliary stricture is one of the most significant complications in liver transplant recipients. The etiology of this complication is multifactorial, and especially in LDLT, the presence of tiny, multiple ducts can contribute to a higher incidence of biliary stricture than that encountered in deceased donor liver transplantation. Although the relationship between the presence of multiple ducts and the incidence/severity of biliary complication remains controversial [6, 7], several studies have indicated that the presence of multiple bile ducts in a graft is a risk factor for biliary complication [1, 2]. Additionally, biliary ischemia is an important, well-documented factor that affects biliary stricture [8, 9]. Considering these factors, surgical innovations are required not only in recipient surgeries, but also in donor surgeries. In order to maintain the blood supply, it is desirable to harvest a large bile duct orifice in the graft, together with a sufficient amount of surrounding tissue. However, there are still several technical and ethical dilemmas associated with this procedure. In particular, in order to obtain a graft containing a single large orifice, it is necessary to cut the bile duct as close as possible to the hepatic hilum, which can lead to biliary stricture in the residual bile duct of the donor. Additionally, in the attempt to cut the bile duct at a precise point, it becomes necessary to expose the bile duct by also dissecting back the surrounding tissue, which can lead to biliary ischemia. The technical innovations described in this study yielded a resolution to these problems. By encircling the hilar plate using a radiopaque marker filament, the cutting point was easily identified, and the surrounding tissue of the hilar plate could be maintained. Under real-time C-arm cholangiography while pulling the filament, the cutting point

was clearly visualized in a three-dimensional image. This procedure using a radiopaque marker filament and C-arm cholangiography was originally introduced by Chen in Taiwan [10]. We then modified the procedure by pulling the filament in order to render the cutting point more clear, as described above. Initially, we adopted this approach for the procurement of right lobe grafts because of the high incidence of multiple bile ducts encountered in these grafts [11]. After the adoption of this novel technique, the incidence of encountering multiple ducts in grafts was significantly reduced without increasing the rate of biliary stricture in donors. Biliary stricture is one of the most significant complications in living donors. According to a survey conducted by the Japanese Liver Transplantation Society, 11% of 1852 donors had biliary leaks and strictures, the majority of which occurred after right lobe hepatectomy; a total of 10 donors underwent surgical revision for biliary complications [12]. To date, we have not observed any biliary complications requiring surgical treatment among our donors. Six cases (7.7%) exhibited minor bile leakage, which in each case was successfully treated by percutaneous drainage alone, i.e., no subsequent biliary strictures developed in any of these donors. With the increasing rate of adult LDLT, several types of graft have been introduced (e.g., left lobe with or without the caudate lobe, right posterior segment graft). In all cases presented here, our novel approach was found to be very effective at enhancing the accuracy of setting the cut point for resection of the bile duct.

One disadvantage of this technique could be possible bile duct injury during encirclement of the hilar plate. Thus, very careful attention should be taken at this step to notice any resistance and thus to avoid forced penetration of the Kelly clamp into the fibrous tissue. Furthermore, it remains important to obtain clear preoperative visualization of the biliary anatomy, thereby to avoid missing any significantly aberrant branching pattern around the hilum. Here, we used magnetic resonance cholangiopancreatography for the preoperative evaluation of the biliary anatomy, and no significant bile duct injuries occurred. In general, the key point of the present procedure is that the hilar plate (i.e., not the bile duct) should be fully exposed before it is marked with the radiopaque marker filament. Thus, the hilar anatomy should be clearly visualized, including assessment of the relationship between the hepatic artery, the portal vein, and the hilar plate. As long as the tissue of hilar plate is preserved, no significant biliary ischemia is likely to occur. Once the encirclement of the hilar plate was completed, this procedure was found to be useful even in cases involving complex bile duct branching patterns. Intraoperative cholangiography just prior to the encirclement of the hilar plate may be helpful in yielding the most secure bile duct division possible.

Whereas donor safety should be the top priority in LDLT, the recipient's outcome is almost equally important in terms of rewarding the donor for his or her devotion to the patient. Our current procedure contributed to a reduction in the incidence of biliary stricture in recipients as well. Randomized and controlled studies would be ideal, but until we have access to such studies, we believe that harvesting a single orifice with sufficient surrounding tissue of bile ducts is a feasible means of performing the most straightforward surgery possible, and this novel approach is expected to contribute to successful outcomes. Moreover, simple anastomosis using a single orifice might facilitate the treatment of any remaining cases involving biliary stricture.

In conclusion, the present procedure of dividing the bile duct during living-donor liver surgery using a radiopaque marker filament and C-arm cholangiography is feasible for avoiding biliary stricture in the donor while maintaining graft quality with sufficient surrounding tissue and reducing the chance of encountering multiple bile duct orifices.

References

1. Testa G, Malagó M, Valentín-Gamazo C, et al. Biliary anastomosis in living related liver transplantation using the right liver lobe: techniques and complications. Liver Transpl. 2000;6:710–4.
2. Gondolesi GE, Varotti G, Florman SS, et al. Biliary complications in 96 consecutive right lobe living donor transplant recipients. Transplantation. 2004;77:1842–8.
3. Belghiti J, Guevara OA, Noun R, et al. Liver hanging maneuver: a safe approach to right hepatectomy without liver mobilization. J Am Coll Surg. 2001;193:109–11.
4. Fan ST, Lo CM, Liu CL, et al. Biliary reconstruction and complications of right lobe live donor liver transplantation. Ann Surg. 2002;236:676–83.
5. Varotti G, Gondolesi GE, Goldman J, et al. Anatomic variations in right liver living donors. J Am Coll Surg. 2004;198:577–82.
6. Ishiko T, Egawa H, Kasahara M, et al. Duct-to-duct biliary reconstruction in living donor liver transplantation utilizing right lobe graft. Ann Surg. 2002;236:235–40.
7. Liu CL, Lo CM, Chan SC, Fan ST. Safety of duct-to-duct biliary reconstruction in right-lobe live-donor liver transplantation without biliary drainage. Transplantation. 2004;77:726–32.
8. Northover JM, Terblanche J. A new look at the arterial supply of the bile duct in man and its surgical implications. Br J Surg. 1979;66:379–84.
9. Yanaga K, Sugimachi K. Biliary tract reconstruction in liver transplantation. Surg Today. 1992;22:493–500.
10. Chen CL. Bile duct reconstruction: proposal from Asian experience. In: 10th annual congress of the international liver transplantation society, June 9–12, 2004, Kyoto, Japan.
11. Takatsuki M, Eguchi S, Tokai H, et al. A secured technique for bile duct division during living donor right hepatectomy. Liver Transpl. 2006;12:1435–6.
12. Umeshita K, Fujiwara K, Kiyosawa K, et al. Japanese Liver Transplantation Society. Operative morbidity of living liver donors in Japan. Lancet. 2003;362:687–90.

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Clinical Transplantation

Honoring the contract with our patients: outcome after repeated re-transplantation of the liver

Eguchi S, Soyama A, Mergental H, van den Berg AP, Scheenstra R, Porte RJ, Slooff MJH. Honoring the contract with our patients: outcome after repeated re-transplantation of the liver.
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Abstract: The aim of this study was to describe the outcome after repeated orthotopic liver re-transplantations (re-OLT) in a population of adults and children, and to determine whether such repeated re-transplantations are an effective treatment or should be considered futile. In a consecutive series of 867 patients, 628 adults and 239 children, who underwent OLT at the University Medical Center Groningen, 23 patients (2.7%), 10 adults and 13 children, underwent more than two re-transplantations of the liver between March 1979 and October 2008. All 23 patients had a second re-transplantation, and seven of them received a third transplant. The overall actuarial patient survival at 1, 5, and 10 yr after primary OLT was 96%, 87%, and 71%, respectively. The overall actuarial patient survival after the second re-OLT was 78%, 73%, and 67%, respectively. Sixteen patients (70%) survived long term. However, for the 23 repeated re-transplantation patients, 76 grafts were used. In a simulation calculation, it was shown that honoring the initial commitment to the 23 patients ultimately led to more surviving patients and less death than if treatment of the original patients was stopped after the first re-transplantation and the remaining grafts were allocated to other primary graft recipients.

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Key words: liver – multiple – repeated – re-transplantation

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The number of orthotopic liver transplantations (OLT) performed is still increasing worldwide each year because of a variety of reasons. The access to this treatment modality for patients with end-stage liver disease has increased as a result of the growing number of liver transplant centers in the world. In addition, the indications for transplantation have widened, and more elderly patients are accepted for transplantation (1, 2). Primary liver transplantation is still hampered by graft failure at a rate of 14–27%, 25–36%, and 38–47% at 1, 5, and 10 yr after OLT, as reported by the European Liver Transplant Registry and various individual centers (1–3). Because of the increasing number of primary transplantations, the need for re-transplantation (re-OLT) has also increased. Although the results of re-OLT are still inferior to those reported after primary OLT, several reports have published improving results of first re-OLTs during the last decade (3–5). Prognostic variables for survival after re-OLT have been identified, including recipient age, era of transplantation, UNOS status, number of previous transplantations, serum creatinine and bilirubin levels, cause of first graft failure, interval to re-OLT, and the donor risk index (4–9). This knowledge makes the proper selection of candidates for re-OLT possible and thereby prevents futile use of the available donor tissue pool. This evolution has contributed significantly to the acceptance of first re-OLTs, despite the limited donor pool.

Only a few reports are available regarding the outcome of second and third re-OLTs. Most of such repeated re-OLTs are reported in overall reviews of single center experiences and do not focus on the outcome of repeated transplantations in individual patients (7, 10, 11). Markman et al. (7) have reported that there were no one-yr

survivors in patients who received more than three grafts. Doyle et al. (12) also reported very poor survival rates after multiple re-OLT. Some individual centers were able to report better results. Pitre et al. (10) published the results of second re-OLTs in eight patients, five infants, and three adults, in 1997. They reported no survivors in three emergency cases, but all five elective cases (62%) survived; however, the survival was at the cost of substantial morbidity. Kumar et al. (11) reported five patients, one child and four adults, with second and third re-OLTs with a one-yr survival rate of 80%. Recently, Akpinar et al. (13) reported patient and graft survival rates at one yr of 72% and 56% after OLT of more than two grafts, with a perioperative mortality of 25%, while Marudanayagam et al. (14) reported that the five-yr survival after second re-transplantation was 40%. During the last decade, the donor shortage has not improved, and shortages are still universal. Therefore, it remains debatable whether the use of multiple grafts for individual recipients is justified (5, 6). For first re-OLT, when performed after selecting patients with prognostic indicators for success, this question is not relevant anymore because of acceptable survival results after the first re-OLT (3–6). However, for repeated re-OLTs, this question remains relevant. The aim of this paper was to report the results, in terms of survival, of repeated (second and third) re-OLTs in adults and children performed at the University Medical Center Groningen (UMCG) between March 1979 and October 2008.

Patients and methods

Multiple re-transplant patients were defined as patients who received more than two re-OLTs during the study period. Pediatric patients were defined as patients younger than 17 yr of age. During the study period, 867 patients, including 628 adults and 239 pediatric patients, underwent 1041 OLTs at the UMCG. In Table 1, an overview is given concerning the re-OLTs performed during that period. All cases of re-OLT were discussed before being listed by an internal review board composed of surgeons, (pediatric) hepatologists, anesthesiologists, and transplant coordinators with regard to the general status, performance status, renal function, infectious complications, and technical feasibilities of the re-OLT procedure. Patients with non-compliance, active infection outside the liver, or poor cardiac and pulmonary function were excluded for re-OLT.

As can be observed in Table 1, 144 (16.6%) of the 867 patients needed a first re-OLT. Twenty-three (2.7%) of the 867 patients (10 adults and 13 pediatric patients) underwent a second re-OLT and formed the study group. Seven (30.4%) of these 23 patients (four adults and three children) needed a subsequent third re-OLT. Multiple re-OLTs were performed in 10 (1.5%) of 628 adults compared to 13 (5.4%) of 239 children ($p = 0.004$).

The median follow-up of the patients since their primary OLT was 115 months (50–224 months) for adults and 112 months (8–204 months) for children.

Perioperative care

Only grafts from hemodynamically stable ABO identical or compatible brain dead donors with normal or near normal liver functions were accepted for re-OLT. Grafts were retrieved according to standard techniques. In case a graft needed to be reduced or split for re-OLT in a child, the criteria set by the Ville de Goyet were used for donor selection (15). The majority of the grafts were preserved in University of Wisconsin Solution, with a few exceptions before 1989, when the Euro Collins solution was used in our program. Grafts were implanted with the conventional or piggy back technique as reported previously by our group (16, 17).

Infection prevention (bacterial and viral) in patients with re-OLTs was essentially the same as

Table 1. Overall liver transplantation experience UMCG in the period March, 1979 till October, 2008

	Total		Adults		Children	
	Patients	Transplants	Patients	Transplants	Patients	Transplants
Total experience	867	1041	628	723	239	318
Re-transplantations						
First re-OLT	144 (16.6%)	144	82 (13.1%)	82	62 (26.0%)	62
Second re-OLT	23 (2.7%)	23	10 (1.5%)	10	13 (5.4%)	13
Third re-OLT	7 (0.8%)	7	3 (0.5%)	3	4 (2%)	4

re-OLT, orthotopic liver re-transplantations.

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%,

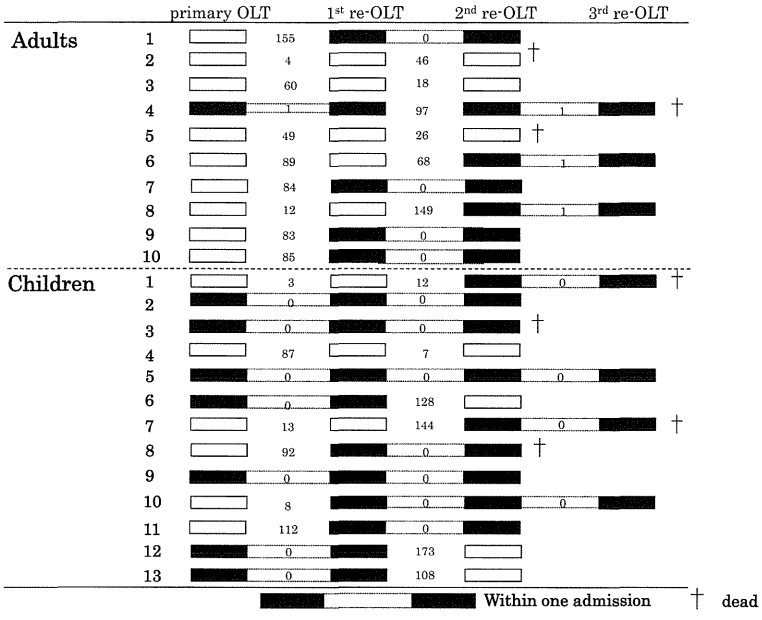

Fig. 1. A schematic presentation of the time interval between each liver transplantation. The combined bars signify orthotopic liver transplantations performed during the same admission. The numbers presented between the bars indicate the number of months between two transplant procedures.

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 ≤ 55 yr and a MELD score of ≤ 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.

References

1. Busuttil RW, Farmer DG, Yersiz H et al. Analysis of long-term outcomes of 3200 liver transplantations over two decades: a single-center experience. Ann Surg 2005: 241: 905.
2. Adam R, Mcmaster P, O'Grady JG et al. Evolution of liver transplantation in Europe: report of the European Liver Transplant Registry. Liver Transpl 2003: 9: 1231.
3. Pfitzmann R, Benscheldt B, Langrehr JM, Schumacher G, Neuhaus R, Neuhaus P. Trends and experiences in liver retransplantation over 15 years. Liver Transpl 2007: 13: 248.
4. Postma R, Haagsma EB, Peeters PMJG, Van Den Berg AP, Slooff MJH. Retransplantation of the liver in adults: outcome and predictive factors for survival. Transpl Int 2004: 17: 234.
5. Azoulay D, Linhares MM, Huguet E et al. Decision for retransplantation of the liver. An experience – and cost-based analysis. Ann Surg 2002: 236: 713.
6. Biggins SW, Beldecos A, Rabkin JM, Rosen HR. Retransplantation for hepatic allograft failure: prognositic modeling and ethical considerations. Liver Transpl 2002: 8: 313.
7. Markman JF, Markowwitz JS, Yersiz H et al. Long-term survival after retransplantation of the liver. Ann Surg 1997: 226: 408.
8. Kim WR, Wiesner H, Poterucha JJ et al. Hepatic retransplantation in cholestatic liver disease: impact of the interval to retransplantation on survival and resource utilization. Hepatology 1999: 30: 395.
9. Northup PG, Pruetto TL, Kashmer DM, Argo CK, Berg CL, Schmitt TM. Donor factors predicting recipient survival after liver retransplantation: the retransplant donor risk index. Am J Transplant 2007: 7: 1984.

10. PITRE J, SOUBRANE O, DOUSSET B et al. Rationale and technical constraints of a tertiary liver transplantation. Liver Transpl Surg 1997: 3: 624.
11. KUMAR N, WALL WJ, GRANT DR, GHENT CN. Patient survival after tertiary liver transplantation. Liver Transpl Surg 1998: 4: 439.
12. DOYLE HR, MORELLI F, MCMICHAEL J et al. Hepatic retransplantation – an analysis of risk factors associated with outcome. Transplantation 1996: 61: 1499.
13. AKPINAR E, SELVAGGI G, LEVI D et al. Liver retransplantation of more than two grafts for recurrent failure. Transplantation 2009: 88: 884.
14. MARUDANAYAGAM R, SHANMUGAM V, SANDHU B et al. Liver retransplantation in adults: a single-centre, 25-year experience. HPB (Oxford) 2010: 12: 217.
15. DE VILLE DE GOYET J. Technique for ex situ cadaveric liver division. In: ROGIERS X, BISMUTH H, BUSUTTIL RW, BROERING DC, AZOULAY D eds. Split Liver Transplantation. Darmstadt: Springer, 2002: 75.
16. MIYAMOTO S, POLAK WG, GEUKEN E et al. Liver transplantation with preservation of the inferior vena cava. A comparison of conventional and piggyback techniques in adults. Clin Transplant 2004: 18: 686.
17. SIEDARS E, PEETERS PM, TEN VERGEET EM et al. Graft loss after pediatric liver transplantation. Ann Surg 2002: 235: 125.
18. KOK T, SLOOFF MJ, THIJN CJ et al. Routine Doppler ultrasound for the detection of clinically unsuspected vascular complications in the early postoperative phase after orthotopic liver transplantation. Transpl Int 1998: 11: 272.
19. VIRVARELLI M, LA BARBA G, LEGNANI C et al. Repeated graft loss caused by recurrent hepatic artery thrombosis after liver transplantation after liver transplantation. Liver Transpl 2003: 9: 629.
20. DESHPANDE RR, RELA M, GIRLANDA R et al. Long-term outcome of liver retransplantation in children. Transplantation 2002: 74: 1124.
21. LERUT J, GORDON RD, IWATSUKI S et al. Biliary tract complications in human orthotopic liver transplantation. Transplantation 1987: 43: 47.
22. VERDONK RC, BUIS CI, PORTE RJ, HAAGSMA EB. Biliary complications after liver transplantation: a review. Scand J Gastroenterol Suppl 2006: 243: 89.
23. TADA S, YAZUMI S, CHIBA T. Endoscopic management is an accepted first-line therapy for biliary complications after adult living donor liver transplantation. Am J Gastroenterol 2007: 102: 1331.
24. THULUVATH PJ, GUIDLINGER MK, FUNG JJ, JOHNSON LB, RAVHILL SC, PELLETIER SJ. Liver transplantation in the United States, 1999–2008. Am J Transplant 2010: 10: 1003.

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

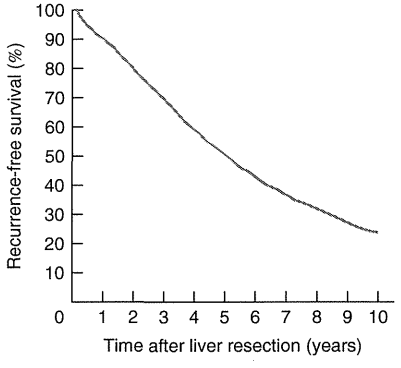
The degree of liver damage was classified as grades A, B and C based on the highest grade containing at least two of five items. Then, if two or more items scoring the same grade occur in the three grades, the higher grade is adopted as the degree of liver damage. ICG-R15, indocyanine green retention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

1 Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997; **349**: 1269–1276.
2 Tsunoda T, Segawa T, Eto T, Izawa K, Tsuchiya R. Long-term survivors after hepatectomy for hepatocellular carcinoma. *J Gastroenterol Hepatol* 1990; **5**: 595–600.
3 Zhou XD, Tang ZY, Ma ZC, Fan J, Wu ZQ, Qin LX *et al.* Twenty-year survivors after resection for hepatocellular carcinoma-analysis of 53 cases. *J Cancer Res Clin Oncol* 2009; **135**: 1067–1072.
4 Fukuda S, Itamoto T, Amano H, Kohashi T, Ohdan H, Tashiro H *et al.* Clinicopathologic features of hepatocellular carcinoma patients with compensated cirrhosis surviving more than 10 years after curative hepatectomy. *World J Surg* 2007; **31**: 345–352.
5 Poon RT, Ng IO, Fan ST, Lai EC, Lo CM, Liu CL *et al.* Clinicopathologic features of long-term survivors and disease-free survivors after resection of hepatocellular carcinoma: a study of a prospective cohort. *J Clin Oncol* 2001; **19**: 3037–3044.
6 The Liver Cancer Study Group of Japan. Primary liver cancer in Japan. Clinicopathologic features and results of surgical treatment. *Ann Surg* 1990; **211**: 277–287.
7 The Liver Cancer Study Group of Japan. *General Rules for the Clinical and Pathological Study of Primary Liver Cancer* (4th edn). Kanehara: Tokyo, 2000.
8 Shimada M, Rikimaru T, Hamatsu T, Yamashita Y, Terashi T, Taguchi K *et al.* The role of macroscopic classification in nodular-type hepatocellular carcinoma. *Am J Surg* 2001; **182**: 177–182.
9 Kokudo N, Makuuchi M. Evidence-based clinical practice guidelines for hepatocellular carcinoma in Japan: the J-HCC guidelines. *J Gastroenterol* 2009; **44**(Suppl 19): 119–121.
10 Bilimoria MM, Lauwers GY, Doherty DA, Nagorney DM, Belghiti J, Do KA *et al.* Underlying liver disease, not tumor factors, predicts long-term survival after resection of hepatocellular carcinoma. *Arch Surg* 2001; **136**: 528–535.
11 Chen JY, Chau GY, Lui WY, Tsay SH, King KL, Wu CW. Clinicopathologic features and factors related to survival of patients with small hepatocellular carcinoma after hepatic resection. *World J Surg* 2003; **27**: 294–298.
12 Hidaka M, Eguchi S, Okudaira S, Takatsuki M, Soyama A, Tokai H *et al.* Multicentric occurrence and spread of hepatocellular carcinoma in whole explanted end-stage liver. *Hepatol Res* 2009; **39**: 143–148.
13 Eguchi S, Hidaka M, Tomonaga T, Miyazaki K, Inokuma T, Takatsuki M *et al.* Actual therapeutic efficacy of

pre-transplant treatment on hepatocellular carcinoma and its impact on survival after salvage living donor liver transplantation. *J Gastroenterol* 2009; **44**: 624–629.
14 Shimada K, Sano T, Sakamoto Y, Kosuge T. A long-term follow-up and management study of hepatocellular carcinoma patients surviving for 10 years or longer after curative hepatectomy. *Cancer* 2005; **104**: 1939–1947.
15 Shirabe K, Shimada M, Kajiyama K, Gion T, Ikeda Y, Hasegawa H *et al.* Clinicopathological features of patients with hepatocellular carcinoma surviving > 10 years after hepatic resection. *Cancer* 1998; **83**: 2312–2316.
16 Eguchi S, Kanematsu T, Arii S, Okazaki M, Okita K, Omata M *et al.* Comparison of the outcomes between an anatomical subsegmentectomy and a non-anatomical minor hepatectomy for single hepatocellular carcinomas based on a Japanese nationwide survey. *Surgery* 2008; **143**: 469–475.

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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,