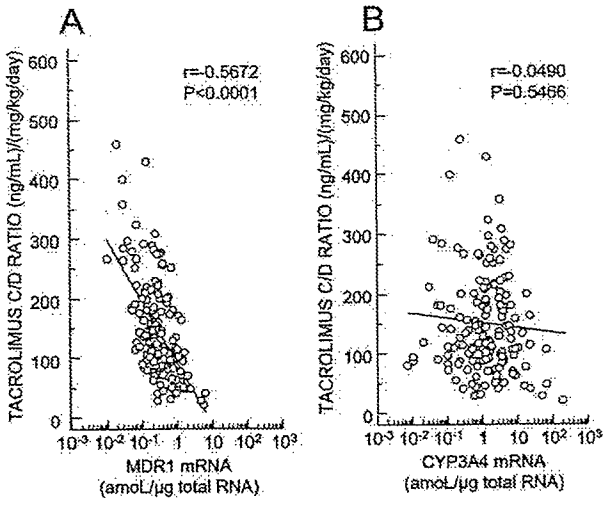

Fig 8. Concentration/dose (C/D) ratio as a function of mRNA expression levels of MDR1 and CYP3A4 in 164 recipients of living-donor liver transplantation. The average C/D ratio in the first 4 days after surgery is compared with the logarithmically transformed mRNA levels of MDR1 (**A**) and CYP3A4 (**B**).

.0001) for the patients whose graft-to-recipient weight ratio was over 1.5 and those whose ratio was under 1.5, respectively (Fig 9, *B* and *C*). However, the coefficient of the correlation between the intestinal MDR1 mRNA level at surgery and the tacrolimus C/D ratio after postoperative day 5 gradually decreased (Table III).

DISCUSSION

Acute cellular rejection, an early complication of orthotopic liver transplantation, occurs in more than 50% of patients[27-29] and can be diagnosed only by means of a liver biopsy.[25] Although it has minimal impact on either death or late graft function, acute cellular rejection should be avoided to reduce the adverse effects of antirejection treatment. The use of high-dose steroids is the first step in both the induction of immunosuppression and the treatment of acute cellular rejection despite side effects such as osteoporosis, recurrent viral hepatitis, and infections.[30-32] The direct association between acute cellular rejection and patient mortality rate is weak,[7] but this episode would be a trigger for other severe complications such as infections, drug-induced renal injury and neurotoxicity, and recurrence of hepatitis with viral amplification in patients receiving the antirejection treatment. In our study the patients categorized in the high-MDR1 group showed a higher frequency of acute cellular rejection until postoperative day 10 and poor survival within 1 year after surgery (Figs 5 and 6). Therefore the individual patients' clinical history should be explored because "acute cellular rejection" might be hidden behind the diagnosis at death. The incidence of acute cellular rejection in our series was 25.6% (42/164 cases) until postoperative day 10 and 32.2% overall (39/121 cases, excluding 32 patients treated with high-dose steroids for other reasons and 11 cases of post-transplant graft liver failure) (Table I). Of 13 patients who died within 1 year after transplantation, 11 were categorized in the high-MDR1 group. The mortality rate of high-MDR1 patients who had acute cellular rejection early on was 25% (6/24 cases), whereas all 15 patients in the low-MDR1 group were alive despite an episode of acute cellular rejection. In addition, the mortality rate of event-free patients was 15% (5/33 cases) in the high-MDR1 group and 4% (2/49 cases) in the low-MDR1 group. Focusing on the patients with acute cellular rejection during the first 10 days after surgery, the high-level expression of intestinal MDR1 was suggested to be associated with poor survival by ^{2} statistics (6/24 cases in high-MDR1 group versus 0/15 cases in low-MDR1 group, P .0352). Although our results were derived from a relatively small number of cases, the intestinal expression level of MDR1 at surgery could be a prognostic factor in patients with acute cellular rejection at an early phase. If the occurrence of acute cellular rejection can be avoided in the high-MDR1 patients, the mortality rate may be decreased to a level comparable to that in the low-MDR1 group. To reduce the frequency of acute cellular rejection early on, the average trough concentration of tacrolimus during the initial 4 days after surgery should be kept above 7 ng/mL, with an initial dosage adjustment that takes into consideration the intestinal expression level of MDR1 at surgery. In addition, extensive exposure to tacrolimus at an early phase may reduce the mortality rate of patients categorized in the high-MDR1 group.

The intestinal adenosine triphosphate–driven efflux pump MDR1 is considered to play an important role in drug pharmacokinetics.[33] This drug transporter prevents the luminal entry of orally administered drugs such as tacrolimus, cyclosporine (INN, ciclosporin), and sirolimus at apical membranes. Since the report by Hoffmeyer et al,[34] several single-nucleotide polymorphisms (SNPs) in *MDR1* affecting expression or function (or both) have been reported. Notably, C3435T and G2677T/A are detected at a relatively high frequency and have been examined for influences on the drug pharmacokinetics and expression level of the gene product.[34,35] We previously found that these SNPs did

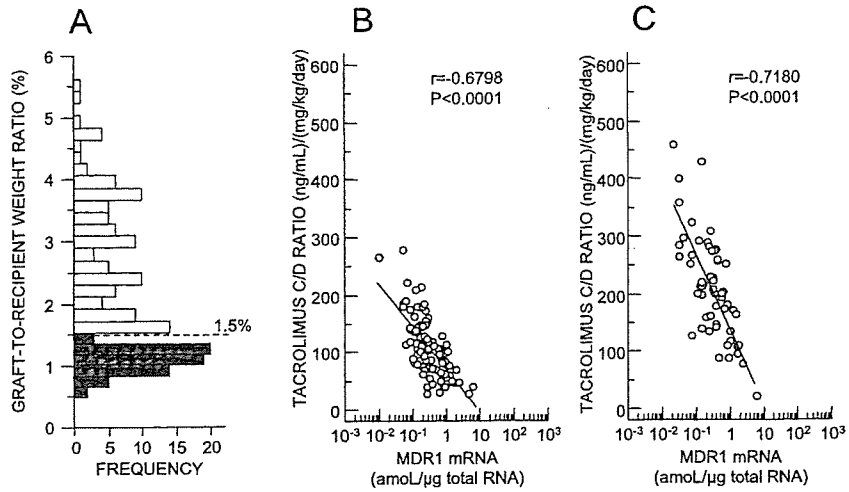

Fig 9. Histogram of graft-to-recipient weight ratio and C/D ratio as a function of mRNA expression levels of MDR1 in 164 recipients of living-donor liver transplantation. A histogram of graft-versus-recipient body weight ratio is shown (**A**). The *dotted line* denotes a graft-to-recipient weight ratio of 1.5. The average C/D ratio in the first 4 days after surgery is compared with the logarithmically transformed mRNA levels of MDR1 in the recipients of living-donor liver transplantation with a graft-to-recipient weight ratio above 1.5 (**B**) and below 1.5 (**C**).

Table III. Coefficient of correlation between intestinal mRNA expression level of MDR1 and tacrolimus concentration/dose ratio in living-donor liver transplantation patients

Postoperative days	*Graft-to-recipient weight ratio 1.5*		*Graft-to-recipient weight ratio 1.5*	
	*r**	*P value*	*r*	*P value*
Between 2 and 4	0.6798 and (n 99)	.0001	0.7180 and (n 55)	.0001
Between 5 and 7	0.3721 and (n 90)	.0003	0.4188 and (n 51)	.0020
Between 8 and 14	0.1598 and (n 98)	.1163	0.0241 and (n 52)	.8660

*Data for patients treated with high-dose steroids including the days of administration and 3 days after withdrawal were excluded.

not affect the intestinal expression of *MDR1* and the tacrolimus C/D ratio in living-donor liver transplant recipients.[21,26] In recipients of renal transplantation, the trough concentrations of cyclosporine and tacrolimus were not influenced by the C3435T SNP.[36,37] In addition, examinations in vitro with a vaccinia virus expression system and mammalian expression system using LLC-PK1 cells indicated that the SNPs in *MDR1* do not affect the membrane expression of P-gp or transport activity of drugs such as digoxin and cyclosporine.[38,39] However, there is little consensus concerning the effect on drug pharmacokinetics by SNPs in *MDR1*.[40] Recently, a meta-analysis by Chowbay et al[41] revealed no significant effect of the *MDR1 C3435T* SNP on either the pharmacokinetics of digoxin or the intestinal expression level of P-glycoprotein. In our study preoperative complications such as cholangitis, hyperbilirubinemia, intestinal congestion, pulmonary hypertension, and renal dysfunction may have affected the expression levels of MDR1, and therefore the direct expression level rather than SNPs of the gene would provide more significant information on liver transplant recipients. On the other hand, CYP3A4 is also expressed in the upper intestinal epithelium and mediates the detoxification of these immunosuppressants at the intestinal wall. Therefore MDR1 and CYP3A4 are considered to provide an "absorptive barrier." We previously demonstrated that the intestinal expression level of MDR1, but not of CYP3A4, was inversely correlated with the tacrolimus C/D ratio in small bowel transplant recipients, as well as patients after living-donor liver transplantation.[18-21] In addition, enhanced expression of MDR1 was associated with a reduction in the bioavailability of cyclosporine in an adult case of living-

donor liver transplantation.[42] In our study we have refined the correlation between the intestinal expression level of MDR1 and tacrolimus C/D ratio during the first 4 days after surgery by taking into consideration the graft-to-recipient weight ratio (Figs 8 and 9). The trough concentration of tacrolimus at postoperative days 3 and 4 was significantly lower in the patients categorized in the acute cellular rejection group than in those in the event-free group (Fig 1). In addition, keeping the initial trough concentration of tacrolimus above 7 ng/mL was suggested to reduce the risk of acute cellular rejection (Fig 3). Therefore the initial adjustment of dosage based on the intestinal MDR1 mRNA level may provide sufficient immunosuppression mediated by tacrolimus with a rapid increase in the blood concentration to around the target range (7 ng/mL) and help to reduce the frequency of acute cellular rejection.

Some risk factors for acute cellular rejection after liver transplantation such as primary disease, Child's classification, and polymorphisms of several cytokines have been postulated.[43,44] These were considered to be congenital factors for patients receiving living-donor liver transplantation, and there is no individualized treatment to reduce the occurrence of acute cellular rejection in patients categorized in the high-risk group. In this study we have found that both the postoperative blood concentration of tacrolimus and the intestinal mRNA level of MDR1 at surgery are significant risk factors for acute cellular rejection early on (Figs 3 and 5 and Table II). However, these risk factors are relatively acquired issues and can be overcome by maintaining the trough concentration of tacrolimus above 7 ng/mL for at least the first 4 days after surgery. In addition, the intestinal expression level of MDR1 at surgery would be a simple pharmacokinetic marker with which to adjust the initial dosage of tacrolimus after living-donor liver transplantation. Therefore quantification of mucosal MDR1 expression may provide for individualization of the dosage regimen of tacrolimus, especially the initial dosage. In this study most of the tacrolimus concentrations were below 10 ng/mL, especially in the acute cellular rejection group (Figs 1 and 7, *B*). To avoid adverse reactions, doctors might be reluctant to raise the dose of tacrolimus in patients with acute cellular rejection. If we can obtain jejunal biopsy specimens for the quantification of mucosal MDR1, the postoperative immunosuppressant dosage regimen could be established before liver transplantation, enabling the tacrolimus trough level to be reached earlier in patients with or without a high level of intestinal MDR1. Therefore a pretherapeutic determination of the intestinal MDR1 mRNA level was suggested to be useful to predict the initial dosage of tacrolimus required in individual patients and thus reduce the frequency of acute cellular rejection immediately after liver transplantation.

In this study we have confirmed that a high expression level of intestinal MDR1 is a prognostic factor for recipients of living-donor liver transplantation (Fig 6, *A*). Although that of CYP3A4 was also associated with poor survival, the odds ratio was not statistically significant. Therefore it was suggested that the intestinal expression level of CYP3A4 was a prognostic factor resulting from some secondary or unknown mechanism. The intestinal expression level of MDR1 was clearly related to the oral clearance of tacrolimus until postoperative day 4 and the occurrence of acute cellular rejection up to postoperative day 10 (Figs 5, *A*, 8, and 9 and Tables II and III). The significant association between the high level of intestinal MDR1 and the 1-year patient survival rate might be explained at least partly by the prognostic significance of early exposure to immunosuppressive therapy after liver transplantation. Therefore medication during ICU care may be critical to survival, as well as the occurrence of acute cellular rejection. The molecular and immunologic mechanism(s) behind these phenomena should be clarified.

The grafted liver mass gradually regenerated after surgery. Fukudo et al[16] demonstrated kinetically that the clearance of orally administered tacrolimus improved or increased (or both) in the postoperative period. In our study the coefficient of the correlation between the intestinal MDR1 level and the C/D ratio of tacrolimus decreased from postoperative day 5 (Table III). This background and our results suggested that hepatic function and the interindividual variation in the rate of graft liver regeneration were associated at least in part with the reduced contribution of the intestinal MDR1 or large intraindividual variation in the pharmacokinetics of tacrolimus after surgery. Surrogate markers relating to the enzymatic activity associated with the interindividual and intraindividual variation in graft liver function after living-donor liver transplantation are needed.

In conclusion, we have advanced our previous finding that the enterocyte mRNA expression level of MDR1 was a simple and useful pharmacokinetic factor for tacrolimus, especially for adjusting the initial dosage in living-donor liver transplant patients. In addition, the average trough concentration of tacrolimus immediately after living-donor liver transplantation should be maintained above 7 ng/mL

for at least 4 days after surgery to prevent acute cellular rejection. Therefore initial dosage adjustment with consideration of the expression level of MDR1 in the small intestine at living-donor liver transplantation may reduce the frequency of acute cellular rejection.

None of the authors has financial or personal relationships that could potentially be perceived as influencing the described research.

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Biliary Reconstruction in Right Lobe Living-Donor Liver Transplantation

Comparison of Different Techniques in 321 Recipients

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Objective: To assess the incidence of biliary complications after right lobe living-donor liver transplantation (LDLT) in patients undergoing duct-to-duct choledochocholedochostomy or Roux-en-Y choledochojejunostomy reconstruction.

Summary Background Data: Biliary tract complications remain one of the most serious morbidities following liver transplantation. No large series has yet been carried out to compare the 2 techniques in LDLT. This study undertook a retrospective assessment of the relation between the method of biliary reconstruction used and the complications reported.

Methods: Between February 1998 and June 2004, 321 patients received right lobe LDLT. Biliary reconstruction was achieved with Roux-en-Y choledochojejunostomy in 121 patients, duct-to-duct choledochocholedochostomy in 192 patients, and combined Roux-en-Y and duct-to-duct choledochocholedochostomy in 8 patients. The number of graft bile duct and anastomosis, mode of anastomosis, use of stent tube, and management of biliary complications were analyzed.

Results: The overall incidence of biliary complications was 24.0%. Univariate analysis revealed that hepatic artery complications, cytomegalovirus infections, and blood type incompatibility were significant risk factors for biliary complications. The respective incidence of biliary leakage and stricture were 12.4% and 8.3% for Roux-en-Y, and 4.7% and 26.6% for duct-to-duct reconstruction. Duct-to-duct choledochocholedochostomy showed a significantly lower incidence of leakage and a higher incidence of stricture; however, 74.5% of the stricture was managed with endoscopic treatment.

Conclusions: The authors found an increase in the biliary stricture rate in the duct-to-duct choledochocholedochostomy group. Because of greater physiologic bilioenteric continuity, less incidence of leakage, and easy endoscopic access, duct-to-duct reconstruction represents a feasible technique in right lobe LDLT.

(*Ann Surg* 2006;243: 559–566)

Biliary tract complication remains one of the most serious morbidities following liver transplantation, with an incidence of 10% to 30% in deceased liver transplantation.[1–4] It has been reported that the pathogenesis of biliary leakage and stricture in deceased liver transplantation were related to preoperative patient condition, blood type incompatibility, ischemic time, hepatic artery complications, and cytomegalovirus (CMV) infection.[5–9] The published data have also suggested that the frequency of biliary complications is higher in post-living donor liver transplantation (LDLT) compared with deceased liver transplantation.[10,11] Major concerns are early leakage and late stricture at the anastomotic site, which are associated with technical, anatomic, or microcirculatory considerations. Particularly in the recipient with "small-for-size" graft or deteriorated preoperative status, early biliary complications readily result in a fatal outcome, and these conditions themselves may increase the risk of complications.

There remains considerable disparity in the reported cases with regard to the incidence of biliary complications after right lobe LDLT, with reported rates ranging from 24% to 60%.[11,12–15] In right liver graft, current controversy focuses on the selection between Roux-en-Y hepaticojejunostomy and duct-to-duct choledochocholedochostomy. Many technical issues, such as the method of dissection, selection of suture and mode, and the use of stenting tube, are still under discussion. Duct-to-duct is currently our standard technique of choice for biliary reconstruction in right lobe LDLT, with the following advantages over Roux-en-Y choledochojejunostomy: 1) no need for intestinal manipulation, serving as an

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Supported in part by grants from the Scientific Research Fund of the Ministry of Education and by a Research Grant for Immunology, Allergy and Organ Transplant from the Ministry of Health, Labor and Welfare, Japan.

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ISSN: 0003-4932/06/24304-0559
DOI: 10.1097/01.sla.0000206419.65678.2e

anatomic barrier to reflux of enteric contents into the biliary tract, and it may theoretically decrease the risk of ascending cholangitis and the morbidity is reduced even when early anastomotic leakage occurs; 2) technically faster and easier than Roux-en-Y; and 3) the physiologic bilioenteric continuity enables good endoscopic access postoperatively.[16,17]

This report describes surgical trials for biliary reconstruction in 321 consecutive right lobe LDLT, focusing on technical considerations regarding the biliary anatomy on graft, suture mode and stent tube in duct-to-duct/Roux-en-Y biliary reconstructions during long-term follow-up.

PATIENTS AND METHODS

Between June 1990 and June 2004, 953 patients underwent 1000 LDLTs at Kyoto University Hospital, Kyoto, Japan. Right lobe LDLT was first carried out at our institution in February 1998, and we have since performed 346 right lobe LDLTs. Of these, 25 patients died within 3 months of LDLT and are thus excluded from this study. A total of 321 patients were the subjects of the present study.

The patients were 164 males and 157 females, with a median age of 43.4 years (range, 15.5–70.3 years), and a median weight of 59.9 kg (range, 34.6–99.5 kg). Median model for end-stage liver disease[18] score was 18.0. The indication for liver transplantation was hepatocellular carcinoma in 86 patients, followed by viral hepatitis (n = 57), cholestatic liver disease (n = 57), fulminant hepatic failure (n = 39), biliary atresia (n = 34), metabolic liver disease (n = 9), metastatic liver tumor (n = 3), retransplantation (n = 16), and others (n = 20). Forty patients (12.5%) received blood type incompatible grafts. Thirty patients (9.3%) received right lobe with middle hepatic vein graft. A total of 121 patients (37.7%) received biliary reconstruction using Roux-en-Y and 192 (59.8%) had duct-to-duct anastomosis, while 8 (2.5%) patients underwent combined Roux-en-Y and duct-to-duct anastomosis. After the introduction of duct-to-duct anastomosis in July 1999, patients who had liver disease without extrahepatic biliary tract involvement were candidates for duct-to-duct anastomosis. The median follow-up period was 60 months (range, 7–80 months) in Roux-en-Y choledochojejunostomy and 34 months (range, 7–64 months) in duct-to-duct anastomosis ($P < 0.01$). There were no significant differences in patient characteristics between either group, except for the follow-up period and the patient age. Because of the patient population with biliary atresia in the Roux-en-Y group, the patient age was significantly younger in the Roux-en-Y group ($P < 0.01$) (Table 1).

Immunosuppression consisted of tacrolimus and low-dose steroids.[19] Patients who received blood type incompatible transplants had preoperative plasma exchange or double filtration plasmapheresis to reduce the anti-ABH antibody titer. Prostaglandin E1, cyclophosphamide, and additional steroids were administered from the portal vein or hepatic artery postoperatively.[20,21]

Statistical analysis was performed using the generalized Wilcoxon test. Actuarial survival rate was calculated with the nonparametric Kaplan-Meier method and was compared with the Wilcoxon test throughout the study. — values of less than 0.01 were considered significant.

TABLE 1. Patient Characteristics

Characteristic	Roux-en-Y (n = 121)	DD (n = 192)	P
Age (yr)	35.2 ± 13.5	48.8 ± 11.3	<0.01
MELD score	16.9 ± 11.4	18.4 ± 10.5	NS
Donor age (yr)	43.1 ± 10.9	41.4 ± 11.9	NS
ABO incompatibility (%)	11.6	13.5	NS
GRWR (%)	1.19 ± 0.29	1.13 ± 0.26	NS
Cold ischemic time (min)	123 ± 103	97 ± 77	NS
Warm ischemic time (min)	42 ± 13	49 ± 17	NS
Operation time (min)	789 ± 192	693 ± 173	NS
Blood loss (g)	7855 ± 10582	6060 ± 8082	NS
Median follow-up period (mo)	60.0	34.0	<0.01

DD indicates duct-to-duct choledochocholedochostomy; GRWR, graft-to-recipient weight ratio; NS, not significant.

The study was approved by the international review board and informed consent was obtained in all the cases.

Donor Operation

Standard right lobe technique was previously described.[12,22,23] Before parenchymal transection, the right lobe was mobilized and the sizeable (>5 mm) right inferior hepatic vein was preserved with a caval cuff for reconstruction. After careful definition of biliary anatomy in the hepatic hilum using intraoperative cholangiography, the right hepatic duct was transected 2 to 3 mm away from the bifurcation. Minimal dissection of pericholedochal tissue was required at this point to maintain blood supply around the hepatic duct, and the hepatic duct was separated with fine scissors. Right-sided liver has a higher incidence of vascular and biliary variant. Overall, 39.6% of grafts had multiple bile ducts in our right lobe LDLT series, which poses a further difficulty in reconstruction.[16,24] The right portal vein and the right hepatic artery were temporally clamped to clarify the parenchymal transection line. An 8-mm Penrose drain was passed between the right hepatic vein superiorly and the portal bifurcation inferiorly to maintain the cutting plane during parenchymal dissection. The end of remnant hepatic ducts were closed with a continuous suture using 6–0 polydioxanone absorbable monofilament, and cholangiogram was performed to ensure that there was no leakage or stricture.

Recipient Operation

Hilar dissection was carefully performed to preserve adequate blood supply of the epicholedodochal arterial plexus and the 2 distinct intramural arteries (3 and 9 o'clock arteries),[25,26] and the bile duct was divided above the hilar bifurcation. Biliary anastomosis was performed with 6–0 polydioxanone absorbable monofilament suture after completion of vascular anastomosis. The graft hepatic duct was anastomosed to Roux-en-Y limb and/or bile duct. When bile ducts in a graft were far apart, they were anastomosed separately. In 8 grafts, the bile ducts were so far apart that both duct-to-duct and Roux-en-Y reconstructions were indi-

cated. If the blood supply of the recipient cystic duct was sufficient and the recipient cystic duct was a better size match, the recipient cystic duct was used for the posterior duct reconstruction. Variations in technical preference remain, and modifications may be necessary to meet anatomic variants. The anastomosis was started at the posterior wall with interrupted or continuous suture, after which the anterior anastomosis was completed. A 4-French polyethylene tube was inserted for anastomotic decompression in some cases.

For internal stent in Roux-en-Y, 2 cm of 18G silicon vascular catheter was placed in the anastomosis. For external stent in Roux-en-Y, the 4-French tube was inserted through the jejunum and the tip was placed through the anastomosis. The stent tube was removed 8 weeks after transplantation.[27]

Biliary complications were diagnosed clinically and radiologically. Biliary leakage was defined by bilirubin level in the bilious ascites higher than the serum level, and stricture was diagnosed by dilated intrahepatic bile ducts with ultrasonography, hepatobiliary scan with Tc-99m Sn-*N*-pyridoxyl-5-methyltryptophan (^{99m}Tc-PMT), and radiologic intervention in all cases.[28]

RESULTS

Overall Incidence of Biliary Complication and Risk Factor

Of 321 right lobe LDLTs, 77 patients (24.0%) experienced 87 biliary complications (leakage: n = 27, 8.4%; stenosis: n = 60, 18.7%). There were no significant differences between the patient with or without biliary complication (n = 77 versus n = 244, respectively) in model for end-stage liver disease score (18.3 ± 9.3 versus 18.0 ± 11.3); donor age (40.9 ± 11.6 years versus 42.5 ± 11.5 years); percentage of blood type incompatibility (16.9% versus 12.3%); graft-to-recipient weight ratio (1.11 ± 0.24% versus 1.16 ± 0.29%); cold ischemic time (112 ± 92 minutes versus 87 ± 67 minutes); and warm ischemic time (48 ± 26 minutes versus 48 ± 16 minutes). However, the respective incidence of hepatic artery complications (28.6% versus 0.4%) and CMV infection (39.0% versus 22.5%) was significantly higher in the patients with biliary complications ($P < 0.01$) (Table 2). Blood type incompatibility was not a significant risk factor in overall right lobe LDLT series.

Overall incidence of biliary leakage and stricture were 12.4% and 8.3% in Roux-en-Y (n = 121), 4.7% and 26.6% in duct-to-duct (n = 192), and 0% in combined Roux-en-Y and duct-to-duct (n = 8), respectively. Duct-to-duct anastomosis showed significantly lower incidence of leakage and a higher incidence of stricture ($P < 0.01$). The onset of biliary leakage and stricture were 19.0 ± 7.7 days (range, 8–35 days; median, 17.5 days) and 12.3 ± 12.2 months (range, 2–36 months; median, 7.5 months) in Roux-en-Y, and 26.5 ± 26.1 day (range, 2–90 days; median, 20 days) and 8.7 ± 5.4 months (range, 2–35 months; median, 8 months) in duct-to-duct (P = not significant), respectively.

TABLE 2. Potential Risk Factor for Biliary Complication in 321 Consequent Right Lobe Living Donor Liver Transplantations

	Biliary Complications		
	Yes (n = 77)	No (n = 244)	*P*
MELD score	18.3 ± 9.3	18.0 ± 11.3	NS
Donor age (yr)	40.9 ± 11.6	42.5 ± 11.5	NS
Blood type incompatibility (%)	13 (16.9%)	30 (12.3%)	NS
GRWR (%)	1.11 ± 0.24	1.16 ± 0.29	NS
Cold ischemic time (min)	112 ± 92	87 ± 67	NS
Warm ischemic time (min)	48 ± 26	48 ± 16	NS
Hepatic artery stenosis/ thrombosis (%)	22 (28.6%)	1 (0.4%)	<0.01
CMV infection (%)	30 (39.0%)	55 (22.5%)	<0.01

GRWR indicates graft-to-recipient weight ratio; CMV, cytomegalovirus; NS, not significant.

Analysis of Biliary Complication According to the Type of Anastomosis

A total of 121 patients received Roux-en-Y biliary reconstruction (Table 3). There was no significant difference in biliary complications among the number of bile ducts in the graft and mode of anastomotic suture (P = not significant). There was a high incidence of biliary complications in the graft with 3 ducts. There was a trend toward a lower incidence of leakage and a higher incidence of stricture in continuous suture, but no significant difference was found among the groups. The patients with external stent (n = 103) showed lower incidence of biliary leakage compared with those with internal stent (n = 5), but this observation did not achieve statistical significance. The incidence of biliary stricture in the patients with external stent was significantly lower than in the patients without stent (n = 13) ($P < 0.01$).

TABLE 3. Biliary Complication in Roux-en-Y Choledochojejunostomy (n = 121)

	n	Leakage (%)	Stricture (%)
No. of graft bile ducts and anastomosis			
1 duct/1 anastomosis	66	7 (10.6)	4 (6.1)
2 ducts/2 anastomoses	64	7 (10.9)	5 (7.8)
3 ducts/1 anastomosis	1	1 (100)	1 (100)
Mode of anastomosis suture			
Interrupted	68	10 (14.7)	5 (7.4)
Continuous	48	4 (8.3)	5 (10.4)
Posterior: continuous/anterior: interrupted	5	1 (20.0)	0 (0.0)
Stent use for biliary reconstruction			
No stent	13	3 (23.1)	3 (23.1)
Internal stent	5	3 (60.0)	2 (40.0)
External stent	103	9 (8.7)	5 (4.9)*

*$P < 0.01$.

TABLE 4. Biliary Complication in Duct-to-Duct Choledochocholedochostomy (n = 192)

	n	Leakage (%)	Stricture (%)
No. of graft bile ducts and anastomosis			
1 duct/1 anastomosis	117	8 (6.8)	38 (32.4)
2 ducts/1 anastomosis	32	0 (0.0)	5 (15.6)
2 ducts/2 anastomoses	41	0 (0.0)	7 (17.0)
3 ducts/1 anastomosis	1	1 (100)	1 (100)
3 ducts/2 anastomoses	1	1 (100)	0 (0.0)
Mode of anastomosis suture			
Interrupted	25	2 (8.0)	9 (36.0)
Continuous	148	7 (4.7)	37 (25.0)
Posterior: continuous/anterior: interrupted	19	1 (5.3)	5 (26.3)
Stent type for biliary reconstruction (12)			
No stent	6	1 (16.7)	2 (33.3)
Cystic drainage	16	2 (12.5)	6 (37.5)
Cystic stent	9	0 (0.0)	2 (22.2)
External stent	163	7 (4.3)	41 (25.1)

Duct-to-duct biliary reconstruction was achieved in 192 cases (Table 4). If we focus on blood type incompatibility in biliary complication with duct-to-duct reconstruction, leakage and stricture was observed in 11.5% and 38.5% of the patients with blood type incompatibility; the incidence of biliary complications was significantly higher in duct-to-duct patients with blood+ type incompatibility ($P < 0.01$).

In 117 recipients (60.9%) of duct-to-duct anastomosis, the common bile duct was used to perform the reconstruction with a single right bile duct. In 11 of 117 patients with single duct-to-duct anastomosis (9.4%) and 8 of 41 patients with 2 anastomoses for 2 ducts (19.5%), a small incision (1–2 mm) in the anterior wall of the graft bile duct was made to accommodate the size mismatch. In 5 patients with one anastomosis for 2 ducts (15.6%), a ductoplasty was performed to enable a single anastomosis to the recipient common bile duct. In 6 of 41 patients with 2 anastomoses for 2 ducts (14.6%), the recipient cystic duct was used to perform the posterior duct reconstruction for better size matching. Two of them (33.3%) had biliary stricture at 2 and 6 months after transplantation. In another case with 2 ducts, the ducts were anastomosed to the recipient left and right hepatic ducts. Totally, there was no significant difference in biliary complications among the number of bile ducts in the graft and mode of anastomosis suture in duct-to-duct reconstruction. However, if the graft had 3 ducts, there was a high incidence of biliary complication.

In 188 cases, the biliary stent tube was inserted for anastomotic decompression in duct-to-duct anastomosis. For cystic drainage (n = 16), the stent was inserted through the remaining cystic duct and pushed downward into the recipient common bile duct. For cystic stent (n = 9), the tube was inserted through the remaining cystic duct and was placed through the anastomosis as a splint. For external stent (n = 163), the tube was placed through the anastomosis and was pulled out through the common bile duct.[16] There was no significant difference in biliary complications according to the type of biliary stent in duct-to-duct reconstruction. If we compare the incidence of anastomotic complication in single duct-to-duct reconstruction (n = 117), the incidence of biliary leakage and stricture was 10.0% and 40% in interrupted suture, 7.2% and 31.3% in continuous suture, 0% and 28.6% in combined interrupted and continuous suture (P = not significant), respectively. Also, the use of the stent tube did not reduce biliary complications in single duct-to-duct anastomosis.

Clinical Outcome of Patients After Biliary Complication in Roux-en-Y Hepaticojejunostomy

The clinical outcome of the patients with biliary complications in Roux-en-Y reconstruction is summarized in Figure 1. Two patients with bile leaks and one with biliary stricture died of sepsis. Biliary leakage was first treated with percutaneous drainage. When the amylase level of aspirated fluid was high or the patient's condition was critical, relaparotomy was indicated. Because the anastomosis appeared to be too fragile for revision, we put drains and carried out a Roux-en-Y enterostomy to isolate/rest the biliary anastomosis (Roux-en-Y diversion). Five patients received Roux-en-Y diversion. The enterostomy was removed after the leak had

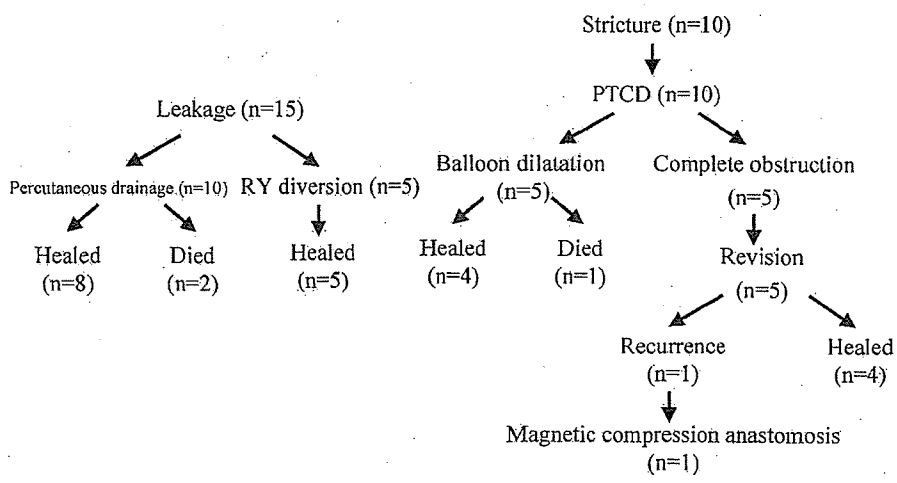

FIGURE 1. Summary of clinical outcome after biliary complications in Roux-en-Y choledochojejunostomy. PTCD, percutaneous transhepatic cholangiography and drainage.

been successfully treated. Two patients died of septic complication after biliary leakage at 14 and 3 months after transplantation.

Four of the 10 biliary strictures were secondary to biliary leakage. Anastomotic stricture was initially managed with percutaneous transhepatic cholangiodrainage (PTCD). Five patients were successfully treated with balloon dilatation. Five patients (50%) with complete anastomotic obstruction required surgical revision. One patient developed biliary stricture after surgical revision and was treated with magnetic compression anastomosis between the hepatic duct and Roux-en-Y loop, as proposed by Yamanouchi et al.[29] One patient with biliary stricture died of sepsis after several courses of PTCD and balloon dilatation 11 months after transplantation. One patient who underwent revision surgery for biliary stricture died of recurrence of hepatocellular carcinoma 30 months after transplantation.

Clinical Outcome of Patients After Biliary Complication in Duct-to-Duct Choledochocholedochostomy

Figure 2 shows clinical outcome of the patients with biliary complications in duct-to-duct reconstruction. In patients with biliary leakage, endoscopic retrograde nasobiliary drainage (ENBD) was indicated as an initial treatment. Four of the 10 patients with biliary leakage required conversion to Roux-en-Y (n = 3) or reoperation with duct-to-duct reconstruction (n = 1). One patient with a blood type incompatible graft died of sepsis 11 months after transplantation. Five of 10 patients were successfully treated with ENBD.

Six of the 51 biliary strictures (15.7%) were secondary to biliary leakage. Initially, anastomotic stricture was referred for endoscopic retrograde cholangiography (ERC). Thirteen of 51 patients (25.5%) could not receive endoscopic treatment because of the difficulty in accessing the papilla of Vater and the difficulty of passing a guidewire through the tight anastomotic stricture. All of them required PTCD. Consequently, 5 patients underwent revision surgery with Roux-en-Y reconstruction to repair the stricture. Two patients with tight anastomotic stricture were closely observed for a week with PTCD for anastomotic decompression, and were successfully treated with endoscopic retrograde biliary drainage (ERBD). Eight patients were treated with ERC balloon dilatation without placing inside stents. One patient died of sepsis secondary to chronic cholangitis 5 months after transplantation. The remaining 27 of 51 patients (52.9%) were treated by placing inside stents endoscopically above the sphincter of Oddi. One patient with a blood type incompatible graft underwent conversion to Roux-en-Y after ERBD because of acute cholangitis and hemobilia. As shown in Figure 2, 9 of 51 patients (17.6%) with duct-to-duct anastomotic stricture required surgical revision. The need for surgical revision due to biliary stricture tended to be lower in the duct-to-duct group compared with the Roux-en-Y group (50.0%), but this did not reach statistical significance ($P = 0.03$).

DISCUSSION

Right-lobe LDLT can provide an adequate graft size to compensate for the metabolic demands in most adult recipients, and the clinical outcome has improved in our series.[22] Among the controversies in right lobe LDLT, techniques of biliary reconstruction remain an open question. Right-sided liver has a higher incidence of vascular and biliary variants, this was explained by the relative consistency between the left umbilical vein and the liver. Multiple biliary orifices are encountered in 26.0 to 39.6% of the cases, which presents a further difficulty in reconstruction in right lobe LDLT.[16,24,30] For safe biliary reconstruction, precise evaluation of the biliary anatomy is essential.

The method for preoperative or intraoperative biliary duct evaluation remains a controversial topic for discussion. We have performed preoperative biliary duct evaluation with three-dimensional drip infusion cholangiographic computed tomography (CT) or magnetic resonance (MR) cholangiography in the evaluation of the potential donor. Although it provides adequate anatomic information of the biliary system, adaptation of these valuable methods for potential donor candidates is not always possible because of the risk of allergic reaction to contrast medium and the cost. In our experience, intraoperative cholangiography is an adequate and convenient way to evaluate the donor biliary tree.

The blood supply for biliary anastomosis is a major concern in LDLT. The arterial blood supply of the biliary system has been described by several investigators. A previous study using fine casts showed that 60% of the arterial

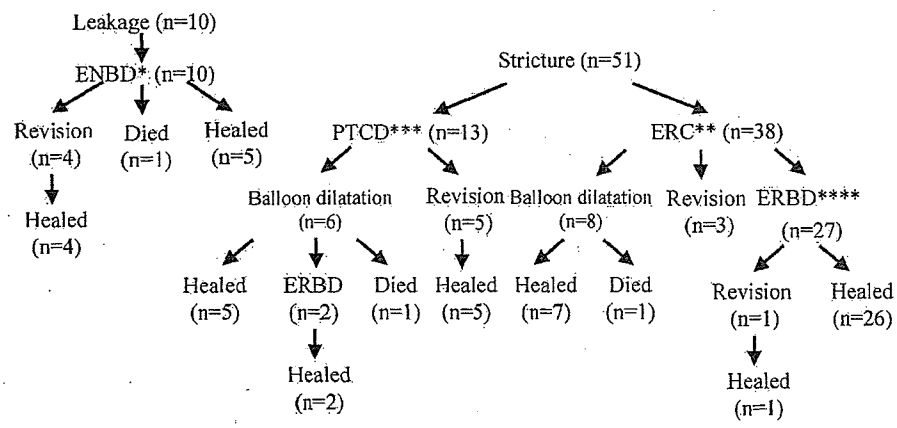

FIGURE 2. Summary of clinical outcome after biliary complications in duct-to-duct choledochocholedochostomy. ENBD, endoscopic nasobiliary drainage; ERC, endoscopic retrograde cholangiography; PTCD, percutaneous transhepatic cholangiography and drainage; ERBD, endoscopic retrograde biliary drainage.

supply for the bile duct comes from the caudal side through periduodenal arteries, 38% from the cranial side and only 2% from the hepatic artery itself. The 3 o'clock, 9 o'clock, and retroportal arteries give rise to multiple arteriolar branches, which form a free anastomosis within the wall of the bile duct.[26] In the absence of any attachments in transplanted liver recipients, the blood supply to the graft bile duct is derived solely from the hepatic artery. Histologic examination of disrupted duct-to-duct reconstruction often shows the loss of 3 o'clock and 9 o'clock intramural arteries on the recipient side (Fig. 3). Preservation of periductal microcirculation in the recipient duct and excellent hepatic artery reconstruction might be a key factor for successful duct-to-duct anastomosis.

Our current study confirmed that arterial complications, CMV infection, and blood type incompatibility were significant and important etiologic variables in biliary complications.[16,27] We do not use prophylactic administration of ganciclovir. However, the results of this study underline the importance of prophylaxis. In our LDLT program, a blood type incompatible graft was unavoidable in 12% of the recipients.[21] Despite the application of preoperative plasma exchange, splenectomy, and enhanced immunosuppression, the 5-year survival rate in adult patients was less than 50% and nearly 70% of the adult patients had biliary complications. We started the intrahepatic arterial immunosuppression protocol from December 2001 and the preconditioning regimen with anti-CD20 monoclonal antibody infusion from April 2004. Although it is still a tentative trial, these protocols have dramatically improved the outcome, with a 1-year graft survival rate of 85.7% and a biliary complication rate of 38.8%.[31]

There is still no consensus among transplant surgeons with regard to the type of biliary reconstruction in right lobe LDLT. Recently, the use of duct-to-duct reconstruction has been increasingly reported in LDLT.[12,14,16,32] We have reported our initial experience of 51 cases of duct-to-duct biliary reconstruction and concluded that it represents a useful technique for right lobe LDLT.[16] In July 1999, duct-to-duct reconstruction became the first choice for biliary reconstruction in our institution. In the series reported here, duct-to-duct technique had a lower incidence of biliary leakage. In cases of biliary leakage with duct-to-duct, peritoneal contamination from intestinal contents was minimized. In addition to the physiologic bilioenteric continuity and later good access by endoscopy, duct-to-duct reconstruction has an advantage over Roux-en-Y that the morbidity is reduced even when early anastomotic leakage occurs.

Biliary stricture was encountered in 26.6% of the patients with duct-to-duct reconstruction in this series, which was significantly higher than the Roux-en-Y group (4.7%). Although strictures seemed to develop more frequently in the duct-to-duct group, the requirement for surgical revision tended to be lower in that group. Because of easy access and imaging through endoscopy, 38 of 51 patients (74.5%) could be treated with ERC. Once ERBD was initiated, 26 of 27 patients (96.3%) were successfully treated. Recently, Gondolesi et al reported the largest Western experience with biliary complications in right lobe LDLT, and demonstrated that duct-to-duct reconstruction had higher incidence of stricture (31.7%) and lower incidence of leakage (16.3%), while the opposite was true following Roux-en-Y reconstruction (7.3% and 18.2%). Also, they recommended early and aggressive use of interventional treatment of biliary complications.[32] We agree with this suggestion that early interventional treatment could avoid further operative intervention. Endoscopic biliary intervention is useful for most anastomotic strictures. Unless the anastomotic site is completely necrotic, insertion of a long-term short stent is very effective in securing bile drainage without increased risk of ascending cholangitis.[17]

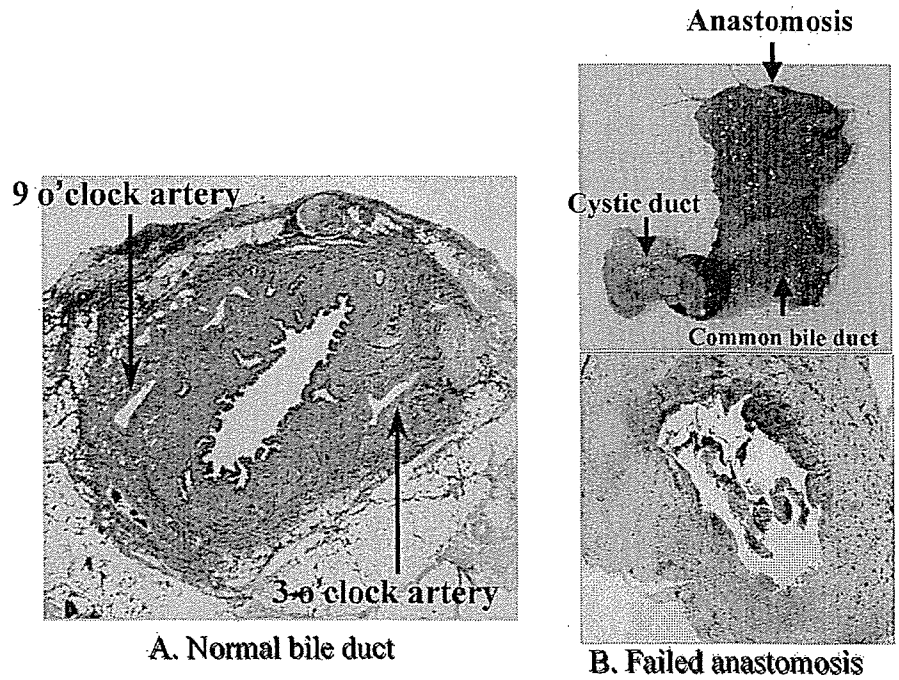

FIGURE 3. Histologic examination of the failed duct-to-duct choledocho-choledochostomy often shows the loss of the 3 and 9 o'clock arteries on the recipient side. Preservation of periductal microcirculation on the recipient side is a key factor for successful anastomosis. A, Normal common bile duct with patent 3 and 9 o'clock intramural arteries. B, Failed duct-to-duct choledochocholedochostomy with loss of 3 and 9 o'clock intramural arteries.

Variations in technical preference remain and modifications may be necessary to take account of anatomic variants in biliary reconstruction. Biliary complications seemed to develop more frequently in graft with multiple bile duct; however, this did not reach statistical significance in the present series. Duct-to-duct reconstruction is safely applied even in multiple bile duct reconstruction with plasty of the graft bile duct or with combined duct-to-duct and Roux-en-Y anastomosis. Contrary to an old concept, duct-to-duct reconstruction has been successfully performed even with the recipient cystic duct,[33] although the incidence of stricture in the cystic duct anastomosis was revealed to be high in our series (33.3%), and not just in a few left lobe grafts.[34]

With regard to biliary morbidity according to the reconstruction method used, we did not find any conclusive tendency to favor any mode or suture. The use of synthetic monofilament suture material was reported to be feasible for biliary reconstruction because of reduced tissue reaction by synthetic materials, as well as bacterial adherence.[35] The Paul Brousse group recommended nonabsorbable suture rather than absorbable material because the resorption of the latter might induce local inflammation and subsequent stenosis.[36] Trends remain in the Roux-en-Y group toward lower incidence of stricture in interrupted suture and lower incidence of leakage in continuous suture in the present study. Our current preference is the use of 6–0 or 7–0 nonabsorbable running suture at the posterior wall and interrupted suture at the anterior wall.

Stenting of the anastomosis is another topic for discussion in LDLT. The rationale of stent is the maintenance of biliary flow despite swelling of anastomosis and easy access for control cholangiography in case of suspected leakage or stricture.[37] The external stent tends to reduce biliary complication in the Roux-en-Y reconstruction, which was consistent with our previous series of 400 pediatric LDLTs.[27] Although our preliminary right lobe with duct-to-duct series demonstrated that the external stent significantly reduced the incidence of biliary stricture,[12,16] overall incidence of biliary stricture was considerably high (26.6%) in long-term follow-up. Scatton et al reported that employment of a T tube increased incidence of biliary complications and recommended the performance of duct-to-duct without a T tube in deceased liver transplantation.[38] The most frequent complication was leakage after T tube removal. We do not experience leakage after removal of 4-Fr biliary tube in the present series. To confirm this finding, while we formerly used a small stent tube, we ceased to use it from July 2004 and are monitoring the results.

CONCLUSION

Duct-to-duct biliary reconstruction in right lobe LDLT appears to be a feasible option with better endoscopic access for treating biliary stricture. Long-term observation may be necessary to collect sufficient data for the establishment of this treatment modality. It is hoped that increased experience and continuing refinements of the technique will lead to improved outcomes in right lobe LDLT.

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LETTER TO THE EDITOR

The use of radial artery interpositional graft between recipient splenic artery and graft artery in living donor liver transplantation

doi:10.1111/j.1432-2277.2006.00386.x

Living donor liver transplantation (LDLT) has become an established treatment for adult patients with end-stage liver disease, including those with hepatocellular carcinoma (HCC). Many of these patients with HCC have undergone various therapies prior to liver transplantation, including transcatheter arterial embolization (TAE) [1].

Repeated TAE can injure the hepatic artery intima, resulting in difficulties with conventional arterial reconstruction. While sufficient hepatic arterial flow is essential for successful liver transplantation, the graft artery usually is short without a cuff, and arteries available for anastomosis are very limited in LDLT. We report LDLT by using the radial artery interpositional graft between recipient splenic artery and graft artery for an HCC patient with pre-operative hepatic arterial occlusion resulting from frequent TAE.

A 56-year-old man with hepatitis B-related cirrhosis and multiple HCC was referred for LDLT. The tumors had been treated five times with TAE, as well as percutaneous microwave coagulation therapy, following the subsegmentectomy. The patient was categorized as Child–Pugh A (score 6); model for end-stage liver disease score 18; and tumor-nodes-metastasis-based stage III. Computed tomography of the abdomen demonstrated multiple HCC, with the largest having a diameter of 34 mm. Abdominal angiography disclosed complete obstruction of the proper hepatic artery and severe narrowing of the common hepatic artery, although the celiac axis and splenic artery remained intact. Allen's test ensured that both the radial and ulnar arteries fully supplied blood to both hands.

A right lobe graft with the middle hepatic vein was transplanted from the patient's wife. The hepatic artery was unsuitable for arterial reconstruction because of severe intimal dissection and poor blood flow. The recipient's right gastroepiploic artery was dissected to evaluate the suitability for reconstruction, but was extremely thin and showed very poor blood flow. We attempted to dissect the splenic artery for direct anastomosis to the graft, but venous collaterals around the artery interfered with continuing dissection to the distal end of the artery to allow the direct anastomosis. Finally, we decided to use the left radial artery as an interpositional vascular graft between the splenic artery and the hepatic artery of the graft. The recipient splenic artery was divided and anastomosed to the radial artery in end-to-end fashion. The radial artery was then anastomosed end-to-end to the right hepatic artery of the graft. Both anastomoses were carried out under an operating microscope. Patency of the arterial reconstruction was very good, and the patient had an uneventful postoperative course. The patient is well without HCC recurrence and patency of hepatic artery is also well after 12 months follow-up.

Although reports of patients with pre-operative hepatic arterial occlusion undergoing LDLT are few [2], some reports requiring the unconventional arterial reconstruction because of hepatic arterial complication in liver transplantation have described. When the original hepatic artery of the recipient could not be used, an alternative artery such as the splenic [3–5], gastroepiploic [6–8], or left gastric artery [9] was anastomosed directly with a good result. Direct anastomosis without a vascular graft has the advantage of requiring only a single anastomosis. However, the alternative artery for direct anastomosis needs to be straighter and longer than in deceased-donor liver transplantation, as in LDLT the graft artery usually is short while excessive stretching at the site of anastomosis leads to arterial complications.

Other studies have reported successful anastomosis by using the saphenous vein [10], inferior epigastric artery [11], sigmoid artery [12], or radial artery [2,8,13], or the inferior mesenteric artery [14] as an interpositional graft. Although an interposed vascular graft requires a double anastomosis, it can prevent arterial stretching and resolve host versus graft artery size-mismatch problems when optimally selected.

We consider the radial artery to be an optimal interpositional graft in this situation because it offers more adequate length and diameter for hepatic arterial reconstruction [2] than other vascular grafts reported in previous studies. The radial artery now is used often in a coronary artery bypass grafting where it has shown excellent long-term patency compared with saphenous vein

[15]. Further, complications related to its procuring are few and minor, as its removal does not adversely affect the subsequent forearm function or blood flow to a clinically important degree in patients with a negative Allen's test [15]. This is the first report of hepatic arterial reconstruction in LDLT with interposition of a radial artery graft between the graft artery and the recipient splenic artery. The splenic artery must be dissected more length to obtain the adequate length to reach the graft directly in LDLT, if it is used for direct anastomosis, compared with in deceased-donor liver transplantation, but accompanying vessels around it can pose significant difficulties in dissecting the distal end. Even when possible, dissection of the splenic artery up to the distal end may cause pancreatitis, pancreatic necrosis, and chylous ascites [4,10]. The advantage of our strategy is that isolation of the splenic artery involves relatively little difficulty and no aortic cross-clamping, unlike anastomosis with the infrarenal portion of the aorta. As an interposition graft, the radial artery tapers from the proximal to the distal end, reducing size discrepancy at the proximal anastomosis with the splenic artery and the distal anastomosis with the graft artery.

Interposition of the radial artery between splenic artery and graft artery is simple, and appears appropriate as one strategy for arterial reconstruction in LDLT requiring unconventional arterial reconstruction.

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Ⅲ　感染対策

移植に伴う感染症；肝移植患者における感染対策

The management of infection in liver transplant recipients

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◆key words：臓器移植，肝移植，術後感染症，周術期管理

はじめに

臓器移植患者は術前状態不良であることが多く，術前よりimmunocompromised hostと考えられる。また，術後免疫抑制を必要とするため，より綿密な感染対策が必要となる。ここでは肝移植術後感染症を中心に，その術前対策と術後発症時の特徴，診断と治療につき述べる。

肝移植患者における感染症の特徴

肝移植における免疫抑制療法は，ステロイドとcalcineurin inhibitorであるタクロリムスもしくはシクロスポリンの併用が中心であるが，最近ではステロイド減量中止を早める傾向にあり，ステロイドを使用しない症例もある。このような免疫抑制状態であることに加えて，肝移植では感染免疫の中心となる肝臓自体を移植するため，移植により置換された肝が患者体内で安定して機能しはじめるまでは，よりimmunocompromised hostの状態であることを十分に考慮する必要がある。また移植患者では感染が存在しても発赤，腫脹，疼痛といった臨床所見を欠いている場合や，CRPなどの炎症反応の上昇がはっきりしない場合も存在する。このため移植後感染症の診断はしばしば困難であり，発見が遅れることで重症化してしまう可能性もある。このため抗菌薬，抗ウイルス薬の治療的投与のみならず，予防的投与や先取り的治療が必要となることも多い[1]。

また，感染症の種類により，おおまかに術後発症しやすい時期があるため，これを参考に時期に応じて感染対策を行う（図1）。

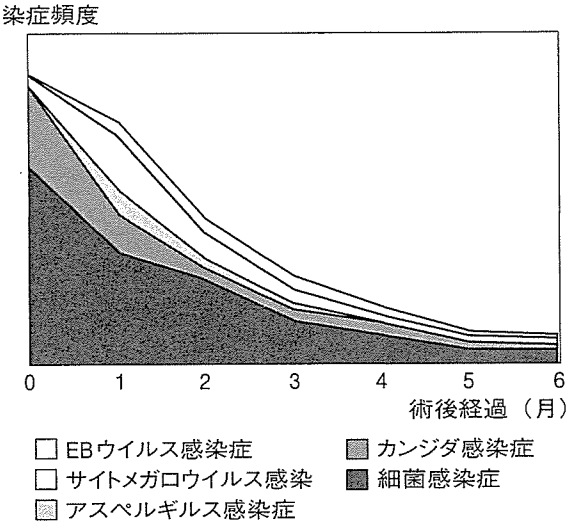

図1　肝移植後感染症のタイムテーブル

術前スクリーニング

移植患者は術前術後にわたりimmunocompromised hostであるため，術前のスクリーニングにより潜在的感染源を同定しておくことが必須となる。

1.　細菌感染スクリーニング

口腔内，尿路，気道につきそれぞれ培養検査，頭部CT，胸部CTなどにより感染スクリーニング診断を行う。とくに齲歯や副鼻腔炎などの感染巣は見逃されやすいので，注意が必要である。感染巣に対しては術前に治療を行い，落ち着いた段階で移植を行うことが原則である。また肝硬変患者では特発性細菌性腹膜炎（spontaneous bacterial peritonitis；SBP）の診断や，過去の結核なども含めた過去の感染既往なども十分に評価する必要がある。SBPが存在する場合は第三世代セフェムによる治療を開始

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する。腹水所見によって好中球の減少と培養の陰性化を確認のうえで移植手術を予定するが，いったん軽快したと思われた後に移植術中に腹膜炎所見の遷延を認めることも珍しくない。

また結核に関しては抗酸菌培養や結核菌 PCR を行い，画像診断とあわせて活動性結核であることを否定する必要がある。結核既往のある患者やツベルクリン反応陽性患者に対する臓器移植後のイソニアジドの予防投与に関しては，欧米の報告ではこれを奨める報告がされている[2]。ただし肝移植レシピエントについてはイソニアジドによる肝障害の頻度が高いとされているため，この点を考慮しわれわれの施設では，肝移植レシピエントに対する移植後イソニアジド予防投与は行っていない。ただし移植後の再活性化は常に念頭に置く必要がある。

2. 真菌感染スクリーニング

真菌感染スクリーニングに関しては臨床所見，画像診断，真菌培養，血清（1→3）-β-D-グルカン値を参考にする。真菌感染の危険因子をもつ患者に対しては，抗真菌薬予防投与に関して総合的に判断する必要がある（表1）。真菌培養に関しては血液培養陽性例など確定診断を得たものに関しては，これが改善するまでは移植手術を行うことはできない。しかし喀痰や便などからの真菌培養陽性例は，多くの場合 colonization と考えられるためとくに対処の必要はないが検出部位が複数に及ぶ場合は，移植後感染の際に強く疑う根拠となる。

3. ウイルス感染スクリーニング

移植後ウイルス感染の原因として，主にサイトメガロウイルスと EB ウイルスがあげられる。成人症例ではほとんどの場合これらのウイルスに既感染であるが，小児症例では未感染であることがある。この場合ドナーが既感染者であると，ドナー由来ウイルス感染症を発症する危険性がある。このため術前にドナーとレシピエントそれぞれについてウイルス抗体のスクリーニングを行う。ドナー陽性，レシピエント陰性という症例では抗ウイルス薬の予防投与を奨める報告もされている[3]。

移植後感染症の特徴と診断治療

1. 細菌感染症

肝移植手術は長時間手術であり輸血量も多くなり，術後も気管挿管期間が長くなる傾向がある。また術前から何らかの感染症治療を行っている症例もある。これらは術後細菌感染の危険因子となる。

表1 術後真菌感染発症の術前危険因子

1. 術前発熱患者
2. 術前抗生物質投与
3. 術前ステロイド投与
4. Child-Pugh score 高値
5. 呼吸器疾患の既往
6. 術前真菌培養陽性

過去の報告例をみると，肝移植後細菌感染症の罹患率は33～68％でありその死亡率は13～77％とされている[4]。また細菌感染症を発症する時期は，術後1カ月以内の早期が多い。起炎菌は *Staphylococcus aureus*, coagulase-negative *staphylococcus*, *Enterococcus faecalis*, *Enterococcus faecium* などのグラム陽性球菌や *Pseudomonas aeruginosa*, 腸内細菌などのグラム陰性桿菌が一般的である。感染部位として多いのは肺，胆道，腹腔内，尿路であり敗血症としての発症も多い。形式は一般腹部手術後の細菌感染症と同様であるが，頻度は非常に高い。一方で中枢神経系感染症はまれである。表2[5]に感染部位と主な起炎菌を示す。

細菌性感染症の治療方針は他の領域と大きく異なるものではなく，塗抹鏡検，培養検査結果をもとに十分量の抗菌薬を十分期間使用することが肝要である。抗菌薬それぞれの特性を十分理解したうえで，感染部位に合わせて選択し使用することが重要である。

以下，主な感染部位別にその特徴と診断治療につき述べる。

1) 敗血症

グラム陽性球菌，グラム陰性桿菌いずれも起炎菌となりうる。カテーテル感染症が一般的であるが肺炎や胆管炎，腹腔内感染からの播種性感染による場合もある。移植患者における敗血症による死亡率は13～36％と高率なので，早急な対応と十分な治療が必要である[4]。具体的にはカテーテル類の抜去と，血液培養結果を得るまでは広域選択性抗菌薬を使用する。カテーテル感染症の可能性が高い場合はとくに MRSA が原因となる可能性があり，欧米ではバンコマイシン（VCM）を加えて治療を開始することを奨める報告もあるが一般的ではない[6]。培養結果が判明した段階で必要ならば感受性のある抗菌薬に変更する。投与期間は解熱後からさらに2週間を原則とされている。明らかなカテーテル感染では若

表2　肝移植患者における主な細菌感染起炎菌

敗血症	呼吸器感染	腹腔内感染	尿路感染
Enterobacteriaceae	Enterobacteriaceae	Enterobacteriaceae	Enterobacteriaceae
Pseudomonas aeruginosa	*Pseudomonas aeruginosa*	*Enterococcus*	*Pseudomonas aeruginosa*
CNS (coaglase-negative *Staphylococcus*)	*Staphylococcus aureus*	*Bacteroides* spp.	*Enterococcus*
Staphylococcus aureus		*Staphylococcus aureus*	*Escherichia coli*
Enterococcus		*Klebsiella*	

干投与期間短縮が可能と考えている。ただし解熱したからといって抗菌薬を中止すると，潜在的な感染源が残存していることがあり，感染再燃の危険性があるため移植患者ではとくにこの点に留意する必要がある。

また，カテーテル感染症予防のため，われわれの施設では中心静脈カテーテルは1週間に1度の新しい部位からの差し替えを原則としている。この他にも術後2～3日目から経腸栄養を導入することにより，中心静脈カテーテルは可及的速やかに抜去するよう心がけている。経腸栄養は腸管由来感染症の予防にも有効と考えている。

2)　呼吸器感染症

肝不全患者の呼吸器感染症の主原因は血行性感染や胸水貯留による拡張障害に伴う経気道感染である。これを予防するため，われわれは抜管後無気肺や胸水貯留を認める症例には，積極的に非侵襲性陽圧換気を導入し，呼吸器合併症の予防に努めている。また，術前肝性脳症を発症している患者や，術後長期挿管患者は誤嚥を起こす危険性が高い。そのような場合は，術後早期に *Pseudomonas aeruginosa* や *Klebsiella pneumoninae*, *Staphylococcus aureus* による肺炎を発症し，しばしば重症化する。このため術後早期の呼吸器感染の起炎菌同定には，術前の監視培養が有効である。ただし，抗菌薬投与に関しては原則として治療として行うべきであり，術前感染のない段階から抗菌薬の全身投与を行うことは，耐性化獲得や真菌感染発症の引き金となるため避けるべきである。

また，移植患者の市中肺炎リスクについては免疫抑制薬が減量できない症例で高くなる。このような場合，術後数カ月以上経過してから発症する。この場合は *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma* などが起炎菌となるが，この時期の肺炎はサイトメガロウイルス肺炎や侵襲性肺アスペルギルス症，カリニ肺炎などウイルス，真菌，原虫による肺炎の可能性も考慮しなければならない。

3)　腹腔内感染症

腹腔内感染症には腹膜炎，腹腔内膿瘍，胆管炎，肝膿瘍などがあげられる。なんらかの腹腔内感染症は肝移植患者の30～50％に発症する[4]。起炎菌はEnterobacteriaceae, *Enterococcus*, *Bacteroides*, *Staphylococcus aureus* などがあげられるが，*Candida* 属により肝膿瘍，腹膜炎が発症することもある。

胆管吻合部には胆管チューブを留置することが多く，留置期間も長期にわたる。とくに胆管空腸吻合を行った症例は，腸管からの上行性感染を引き起こす可能性があり，胆管胆管吻合を行った症例と比較して胆管炎の発生率が高い[7]。また，術後の胆管合併症を併発した症例では，経皮経肝胆管ドレナージや，内視鏡的胆管ドレナージを必要とすることがある。このような症例では胆管炎発症の危険性が高く注意が必要である。

胆道閉鎖症のため肝移植を施行する場合，以前に肝門部空腸吻合術を施行されていることが多い。これらの症例では吻合部から分離される細菌が術後，腹腔内膿瘍や胆管炎の起炎菌となるため，あらかじめ培養検査を行い，より有効な治療につなげるべきである。

2.　真菌感染症

肝移植後真菌感染症は1980年代の米国の報告では患者の約40％に発症するとされているが，われわれの施設での統計では過去2年間，35例中明らかな真菌感染を発症したものは *Candida albicans* によるカンジダ血症を発症した1例のみであった。以下主な真菌感染症についてその特徴と診断治療につき述べる。

1)　カンジダ感染症

Candida による感染症は移植後1カ月以内が多く真菌感染症の原因菌として70－80％を占める。その原因種は *C. albicans*（78％），*C. tropicalis*（8％），*C. glabrata*（7％），*C. parapsilosis*（5％），*C. lusitaniae*（1％）と報告されている[4]。深在性真菌症としてカンジダ血症，尿路感染症，肝膿瘍，脾膿瘍，

胆管炎，腹膜炎の原因となる。*Candida* 属による肺炎は一般的ではない。

・診　断

発熱，全身の倦怠感などであるが非特異的である。血液培養，尿培養，腹水培養などで *Candida* が検出され，臨床所見と一致すればカンジダ感染症と判断してよいだろう。しかし，培養では検出されないことも多く，血液培養を除いて，colonization との鑑別も困難であり診断に苦慮することが多い。そのため，血清（1→3）-β-D-グルカン値も参考にすることでかなり信頼できる診断をつけることができると考えている。術後ハイリスク症例では血清（1→3）-β-D-グルカン測定を定期的に行い，真菌感染の発症に注意する。血清（1→3）-β-D-グルカンについては臨床症状を伴わない単発で軽度の上昇に鋭敏に反応する必要はない一方で，真菌感染症の早期に上昇しない例，さらに偽陽性もあることに十分留意する。確定診断を得ることが困難な場合が多く，実際は先取り的に治療開始する方針としている。

・治　療

C. albicans がもっとも多いことから，感受性の高いフルコナゾール(FLCZ)，もしくはイトラコナゾール（ITCZ）投与が原則となる。重症者に対してはミカファンギン(MCFG)やボリコナゾール(VRCZ)，アムホテリシンB（AMPH）の投与を考慮する。*C. glabrata* に関しては FLCZ への耐性化が問題となるため，*C. glabrata* が証明された段階，もしくは FLCZ に反応しないと判断された段階で MCFG，VRCZ，AMPH への変更を考慮する必要がある[8)9)]。ただし AMPH による腎障害に十分注意するべきであり，この点を考慮し最近では使用頻度が減ってきている。

2）　アスペルギルス感染症

移植後真菌感染の約15～20％であり，発症時期は術後2～6週に多いとされている[4)]。起因菌種は *A. fumigatus* がもっとも多く，感染部位は呼吸器を中心に播種性となることが多い。中枢神経に及ぶこともあり，その場合は予後不良である。

・診　断

培養検査での *Aspergillus* 検出率は低く，診断には肺野条件の胸部 CT が有用である。肺アスペルギルス症は CT で特徴的な浸潤影を呈する。血清（1→3）-β-D-グルカンは感染徴候が明らかになると同時に上昇することが多い。すなわち血清（1→3）-β-D-グルカン陰性は感染の可能性を除外する根拠としては弱く，やはりX線，CT による綿密な評価が重要となる。中枢神経アスペルギルス症は播種性感染と考えられるが，血液培養陽性となる症例はまれである。診断には頭部 CT により膿瘍を認めた場合に疑う必要がある。*Aspergillus* 感染による頭蓋内出血や梗塞により発症することもある。

・治　療

侵襲性アスペルギルス症と判断された場合，以前は AMPH が first choice であったが現在では MCFG や VRCZ が有用と報告されている[10)]。一般的に予後は非常に悪く死亡率は78～98％であるが，MCFG，VRCZ の登場で改善が期待されている。

3.　ウイルス感染症

移植後ウイルス感染の原因には種々のウイルスがあげられるが，ここではサイトメガロウイルスと Epstein-Barr（EB）ウイルスにつき述べる。

1）　サイトメガロウイルス

移植後ウイルス感染の原因としてもっとも多く，レシピエントの20～30％が感染発症する。感染経路はドナーもしくは輸血による移行感染，再燃，初感染である。このなかでサイトメガロ抗体陽性ドナーから陰性レシピエントへの移行感染がもっとも多いと報告されている[11)]。発症時期は術後3～8週間後が多い。発症形式は肝炎，肺炎，腸炎，腹膜炎などが一般的である。

・診　断

原因のはっきりしない発熱，肝機能異常，肺炎症状，消化管出血や下痢などの腸炎症状で発症する。血液検査で白血球減少，リンパ球増多，異型リンパ球の出現，血小板減少を認める。肝生検により核内封入体の証明や，胸部X線，CT による肺炎像の証明，消化管内視鏡による腸管粘膜潰瘍の証明などの臨床所見に，血液，腹水を検体としたサイトメガロウイルスアンチゲネミア測定やサイトメガロウイルス PCR を行い，これらの結果を参考にして総合的にサイトメガロウイルス感染を診断する。このようなアンチゲネミア測定，PCR により早期診断が可能となってきたため，有症状のサイトメガロウイルス感染の頻度はかなり減少してきている。

・治　療

拒絶反応を合併した場合，予後悪化につながるため，免疫抑制薬投与量の減量は軽度にとどめる。静注用ガンシクロビル5 mg/kg を12時間ごと，2週間投与する。副作用として白血球減少，血小板減少に注意する。重症例には高サイトメガロウイルス抗体価グロブリンを投与する。われわれの施設では，

治療効果判定をPCRにて行っている。

また，サイトメガロウイルス抗体陰性レシピエントや，不適合移植により強力な免疫抑制を必要とする症例ではガンシクロビルの予防投与を行うことで，サイトメガロウイルス感染のリスクを下げることができる[3)12)]。

2) EBウイルス

感染経路はサイトメガロウイルスと同じく，移行感染，再燃，初感染である。EBウイルス感染ではpost transplant lymphoproliferative disorder (PTLD) が問題となる。これは免疫抑制薬によるTリンパ球抑制が，Bリンパ球系の異常増殖を引き起こす病態である。

・診　断

感染を起こしても無症状であることも多いが，通常，発熱，リンパ節腫脹，咽頭炎，脾腫などの症状を呈する。血液検査にて白血球減少，血小板減少，異型リンパ球出現を認める。EBウイルスPCRが診断に有効である。PCRはPTLD発症の予測にはならないとされているが，発症の予防を可能するとともに治療効果判定にも有用とされている[13)14)]。

・治　療

免疫抑制薬の減量，重症例では中止が必要である。アシクロビル30～90mg/kg/dayの投与を行う。PTLDに対しては抗癌薬投与が必要となることもある。抗CD20抗体であるリツキシマブ投与が有効とも報告されている[15)]。

まとめ

以上，肝移植を中心に移植後気をつけるべき感染症につき解説した。感染症の種類は多岐にわたり，診断が困難であることも多い。このため，移植患者では術後経過における微細な変化を見逃すことなく，きめ細かい対応をとることで，重大な感染症を未然に防ぐことがもっとも重要である。

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