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生体肝移植後のC型肝炎再発予防を目指したステロイド剤不使用による免疫抑制療法に関する研究

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総括研究報告書

生体肝移植後のC型肝炎再発予防を目指したステロイド剤不使用による免疫抑制療法に関する研究

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研究要旨
当科で生体肝移植を受けたC型肝硬変患者132人の移植後肝炎の再発について検討したところ、肝生検によって診断されたF2以上の線維化を伴う慢性肝炎の再発率は、移植後3年で56%であった。
生体肝移植後肝炎再発防止を目指した新しい免疫抑制療法に関する無作為比較試験は症例数を重ね、全体でこれまで52例が登録され重篤な有害事象はなく研究が進められている。

A. 研究目的

C型肝炎ウィルス(HCV)感染による肝硬変および合併する肝細胞癌は、死亡原因として最も重要な肝疾患であり、その治療法として肝移植の有効性が期待されている。しかし、肝移植後のHCV肝炎再発はほぼ必発であり、肝炎再発に関連するグラフト機能不全のために他の疾患に比べて5年以降の移植後長期予後が有意に不良であることが問題となっている。

肝移植後のHCV肝炎再発の特徴として、ウィルス量が肝移植後に急速に上昇しその値は移植前に比べて非常に高くなること、慢性肝炎から肝硬変への進展が早い、すなわち肝の線維化速度が速いことなどが挙げられ、その原因として移植後免疫抑制療法の影響が考えられている。特に、ステロイド剤はHCVの増殖を促進する可能性が示唆され、移植後HCV肝炎再発防止のためにはこれまでのステロイドを中心とした免疫抑制療法の見直しが必要である。

本邦でも近年、HCV関連肝硬変ならびに肝細胞癌患者に対する成人生体肝移植の実施数が増加している。本研究は、1）当施設で実施したC型肝炎への生体肝移植後の肝炎再発の実態を明らかにする、2）生体肝移植後肝炎再発防止を目指したステロイドフリーによる新しい免疫抑制療法を開発することを目的とする。

B. 研究方法

1）平成11年3月から平成18年5月までに、京都大学移植外科で生体肝移植

を受けたC型肝硬変患者132人を対象として、肝生検結果に基づく移植後C型肝炎の再発について検討した。

2）HCV関連肝硬変患者の生体肝移植後肝炎再発防止を目指した新しい免疫抑制療法の開発を目的としてとして、多施設共同の前向きの無作為比較試験を開始している。その治療プロトコルは従来のタクロリムスとステロイド剤による免疫抑制療法を行う群（A群）と、ステロイド剤を一切使用せずミコフェノール酸モフェチル（MMF）とタクロリムスを使う新しい免疫抑制療法を行う群（B群）の2群に分けられ、両群を比較検討する。この臨床試験に関する倫理面への配慮については、本学および各研究参加施設の倫理委員会の審議を経てその指針を受けている。

C. 研究結果

1）132例の移植後5年生存率は71%で、他の疾患に対して生体肝移植を受けた成人267例の場合の69%と同等であった。移植後stage F2以上の有意な線維化を伴う慢性肝炎の再発は30例に認め、移植後3年累積再発率は56%であった。この有意な線維化進展のリスクファクターの検討では、レシピエントが女性、ドナーが男性などが挙げられた。これまでfibrosing cholestatic hepatitis 2例を含む5例が肝硬変に進展し、2例が死亡、1例が再移植を受けている。

2）平成16年2月から実際に無作為比較試験を開始した。18年12月までに全体で52人が参加登録され、A群またはB群に無作為に割り付けられプロトコルに基づく治療を受けている。これまで試験継続が不可能となる重篤な有害事象は認められておらず、研究計画における安全性は確認されたと考えられる。研究計画において中間解析は行わないことになっているため、肝炎再発予防における有効性の評価はまだ行われていない。

D. 考察

最近欧米での一部の施設において、脳死肝移植に比べて生体肝移植の方が移植後C型肝炎の再発の危険性が高いと報告された。しかし、今回の検討ではstage F2以上の有意な線維化を伴う慢性肝炎の3年再発率が56%、5年生存率が71%と脳死肝移植の報告と比べて遜色はなく、肝炎再発が生体肝移植後の予後に著明な影響を与えることはないと考えられた。

一方、生体肝移植後肝炎再発防止を目指したステロイドフリーによる新しい免疫抑制療法の開発に関する臨床試験は開始して3年になるが、当施設でこれまで参加登録された43例において安全性は確認されており、今後もプロトコル継続は可能であると判断された。

E. 結論

生体肝移植後肝炎再発防止を目指したステロイドフリーによる新しい免疫抑制療法の開発に関する臨床試験は多施設共同の無作為比較試験として立ち上げられ

て 3 年が経過し、本施設以外の他の施設からも症例登録されるようになり、今後は登録症例数の増加と研究の推進が期待される。

F. 健康危険情報

なし

G. 研究発表

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H. 知的財産権の出願・登録状況

なし

別紙４

研究成果の刊行に関する一覧表レイアウト

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Takada Y, et al.	Clinical outcomes of living donor liver transplantation for HCV-positive patients	Transplantation	81	350-4	2006
Kasahara M, Egawa H, Takada Y, et al.	Biliary reconstruction in right lobe living-donor liver transplantation: comparison of different techniques in 321 recipients	Ann Surg	243	559-66	2006
Haga H, et al.	Acute humoral rejection and C4d immunostaining in ABO blood type-incompatible liver transplantation	Liver Transpl	12	457-64	2006
Takada Y, et al.	Living donor liver transplantation as a second-line therapeutic strategy for patients with hepatocellular carcinoma	Liver Transpl	12	912-9	2006
Iwai A, Marusawa H, Takada Y, et al.	Identification of novel defective HCV clones in liver transplant recipients with recurrent HCV infection	J Viral Hepat	13	523-31	2006
Tanaka K, Ozawa K, Teramukai S, Takada Y, et al.	Classification of human liver transplant recipients by their preoperative CD8 T cell subpopulation and its relation to outcome	Liver Transpl	12	792-800	2006
Umeda M, Marusawa H, Ueda M, Takada Y, et al.	Beneficial effects of short-term lamivudine treatment for de novo hepatitis B virus reactivation after liver transplantation	Am J Transplant	6	2680-2685	2006
Yoshizawa A, Takada Y, et al.	Liver transplantation from an identical twin without immunosuppression with early recurrence of Hepatitis C	Am J Transplant	6	2812-2816	2006
Hussein Ali, Watashi K, Hijikata M, Kaneko H, Takada Y, et al.	Serum-derived hepatitis C virus infectivity in interferon regulatory factor-7-suppressed human primary hepatocytes.	J Hepatol	46	26-36	2007

Clinical Outcomes of Living Donor Liver Transplantation for Hepatitis C Virus (HCV)-Positive Patients

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Background. Whether hepatitis C virus recurrence occurs earlier and with greater severity for living donor liver transplantation (LDLT) than for deceased donor liver transplantation (DDLT) has recently become a subject of debate.
Methods. We retrospectively evaluated clinical outcomes for a cohort of 91 HCV-positive patients who underwent LDLT at Kyoto University with a median follow-up period of 25 months.
Results. Overall 5-year patient survival for HCV patients was similar to that for non-HCV patients (n=209) who underwent right-lobe LDLT at our institute (69% vs. 71%). Survival rate of patients without HCC (n=34) tended to be better than that of patients with HCC (n=57) (82% vs. 60%, $P=0.069$). According to annual liver biopsy, rate of fibrosis progression to stage 2 or more (representing significant fibrosis) was 39% at 2 years after LDLT. Univariate analysis showed that female recipient and male donor represented significant risk factors for significant fibrosis. Progression to severe recurrence (defined as the presence of liver cirrhosis (F4) in a liver biopsy and/or the development of clinical decompensation) was observed in five patients.
Conclusions. Postoperative patient survival was similar for HCV-positive and -negative recipients in our adult LDLT series. Rates of progression to severe disease due to HCV recurrence seemed comparable between our LDLT recipients and DDLT recipients described in the literature. Although longer-term follow-up is required, our results suggest that LDLT can produce acceptable outcomes also for patients suffering from HCV-related cirrhosis.

Keywords: Hepatitis C virus, Living donor, Recurrence.

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Chronic hepatitis C virus (HCV) has become a global epidemic, with an estimated 200 million people currently infected worldwide. Nowadays, HCV-related cirrhosis is the most common indication for liver transplantation. However, recurrence of HCV infection is universal and often occurs immediately after transplantation (*1*). The prevalence of chronic hepatitis C in HCV-positive liver transplant recipients is 70–90% after 1 year, and rate of fibrosis progression is accelerated so that 20–40% of patients progress to allograft cirrhosis within 5 years (*2–6*). As a result, graft and patient survival is significantly reduced for HCV-positive recipients compared with HCV-negative recipients (*6–7*).

In Japan, too, HCV-related cirrhosis and hepatocellular carcinoma (HCC) represent the most prevalent liver diseases, and living donor liver transplantation (LDLT) has become a treatment option for patients with these diseases. However, a warning was recently issued by some Western transplant centers that HCV recurrence may occur earlier and with greater severity, and graft loss caused by recurrent HCV may be more frequent for LDLT than for deceased donor liver transplantation (DDLT) (*8–11*). Some suggestions have been offered for mechanisms that could increase graft damage in HCV-infected LDLT recipients (*12*). First, because the right hepatic lobe graft undergoes intense regeneration immediately after LDLT, specific cellular changes occurring during this vigorous proliferative response may facilitate entry of HCV into hepatocytes or promote HCV replication. Second, since most living donors are primary relatives of the recipient, increased genetic similarity and a higher degree of HLA matching between donor and recipient compared with DDLT may affect the severity of recurrent HCV infection. Conversely, more recent studies have reported comparable results between LDLT and DDLT (*13–15*). Such discrepancies may be explained in part by the small numbers of LDLT patients included in these studies, or learning curve effects on recent data associated with increased experience (*16*).

This issue has attracted worldwide attention because, given the shortage of deceased donor organs, increasing numbers of patients are choosing to undergo LDLT. The matter is of critical importance in Japan and countries where almost all liver transplantations use living donor grafts. The present study retrospectively evaluated clinical outcomes for a comparatively large cohort of 91 patients who underwent LDLT for HCV-related cirrhosis at our institute. We investigated the frequency and severity of posttransplant recurrence of chronic HCV hepatitis and examined risk factors in order to clarify the role of LDLT in the treatment of patients with HCV cirrhosis.

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PATIENTS AND METHODS

Patients

Between March 1999 and April 2005, LDLT was performed at Kyoto University on 105 patients with HCV cirrhosis. Of these, 91 patients (61 men, 30 women) who had undergone LDLT by June 2004 and had been followed up for >12 months were included in this study (Table 1). Median age of subjects was 55 years (range, 30–69 years). Median model for end-stage liver disease (MELD) score was 16 (range, 4–33). HCV cirrhosis was accompanied by HCC in 57 patients (63%), including 25 who exceeded Milan criteria. Median MELD scores in groups with and without HCC were 15 (range, 4–33) and 18 (range, 9–33), respectively (P=0.015, Mann-Whitney U test).

All patients were positive for anti-HCV antibody before the operation. Preoperative HCV RNA load, measured using the polymerase chain reaction (PCR) method with an Amplicor HCV assay (Roche Molecular Systems, Pleasanton, CA), was obtained for 74 patients, with a median value of 260 kIU/ml (range: <0.5–2400). Patients treated during the early period, in whom viral load was measured only using DNA probe methods, were considered to lack relevant data. HCV genotype, determined using a system based on PCR with genotype-specific primers (*17*), was: 1b (n=52); 2a (n=6); 2b (n=3); others (n=2); not determined (low viral load, n=3); or not examined (n=25).

LDLT using a right-lobe graft was performed on all except two patients who received left lobe grafts. Operative procedures for donor and recipient surgery have been described elsewhere (*18, 19*). Donors were 52 men and 39 women, with a median age of 40 years (range, 19–64 years). Relationship to the recipient was: child (n=36); spouse (n=34); sibling (n=17); parent (n=1); or other (n=3). ABO blood-type matching was incompatible in 15 cases.

After discharge, patients were scheduled for monthly visits to the outpatient clinic for the first year. Median duration of follow-up was 25 months (range, 1–72 months).

TABLE 1. Preoperative profile and clinical characteristics

Characteristic	Data
n	91
Recipient sex (male/female)	61/30
Median recipient age, years (range)	55 (30–67)
Child-Pugh grade (A/B/C)	2/26/63
Median MELD score (range)	16 (4–33)
Pretransplant HCC (yes/no)	57/34
HCV genotype (1b/2a/2b/others)	52/6/3/2
Median HCV-RNA, kIU/mL (range)	260 (<0.5–2400)
Pretransplant interferon therapy (yes/no)	30/61
Median donor age, years (range)	40 (19–64)
Donor gender (male/female)	52/39
Relation to recipient (related/unrelated)	57/34
ABO blood-type mismatch (yes/no)	15/76
HLA-A,B mismatch (≤2/≥3)	70/21
HLA-DR 2 mismatch (yes/no)	26/65
GRWR ≥1.0% (yes/no)	54/37
Immunosuppression (FK/CyA)	83/6
Steroid-free induction (yes/no)	19/72
Methylprednisolone boluses for rejection (yes/no)	32/59

Immunosuppression

The standard immunosuppression protocol comprised tacrolimus and low-dose steroid (*20*). The target whole-blood trough level for tacrolimus was 10–15 ng/ml during the first 2 weeks, approximately 10 ng/ml thereafter, and 5–8 ng/ml from the second month. Cyclosporine microemulsion was administered instead of tacrolimus for induction immunosuppression in six patients. Steroid therapy was initiated at a dose of 10 mg/kg before graft reperfusion, then tapered from 1 mg/kg/day on day 1 to 0.3 mg/kg/day until the end of the first month, followed by 0.1 mg/kg/day until the end of the third month. After this time, steroid administration was terminated. As an exception, 13 patients received steroid-free tacrolimus monotherapy as an induction procedure in an attempt to reduce HCC recurrence. In addition, four patients were assigned to a tacrolimus plus mycophenolate mofetil (MMF) (without steroid) group in a prospective comparative study started in March 2004 to evaluate the effects of steroid-free immunosuppression on recurrence of HCV. Another two patients transplanted with grafts from an identical twin did not receive any immunosuppressive treatment.

Patients who received ABO blood-type incompatible transplants were treated with preoperative plasma exchange or double-filtration plasmapheresis in order to reduce anti-A or B antibody titers. During the first 3 weeks postoperatively, prostaglandin E1 and additional steroids were administered via the portal vein or hepatic artery (*21*). Cyclophosphamide was also given intravenously for the first 2 weeks, and then orally.

Acute rejection episodes were documented by means of liver histology (*22*) and treated with methylprednisolone boluses if moderate or severe. OKT-3 was used for only one patient. MMF or azathioprine was added for patients who experienced refractory rejections or required reduction of tacrolimus dose due to adverse effects.

Antiviral Therapy

Prophylactic antiviral therapy for HCV was not administered. As a rule, antiviral treatment was used for patients with recurrent chronic hepatitis C. The treatment protocol consisted of interferon α2b ($3–6\times10^6$ units 3 times/week) plus ribavirin (400-800 mg/day orally for the first 6 months), followed by interferon monotherapy for 6 months.

Histological Assessment

A total of 398 liver biopsies were evaluated when patients displayed liver enzyme levels elevated more than two to three times the normal upper limit, or at yearly intervals when informed consent was obtained. Annual follow-up biopsies were obtained from 60 patients at 1 year after LDLT, 34 patients at 2 years, 14 patients at 3 years, 6 patients at 4 years, and 1 patient at 5 years. Biopsy specimens were evaluated by a single pathologist (H.H.) with extensive experience in the pa-

thology of liver transplantation. Necroinflammatory activity (A0-A4) and fibrosis stage (F0-F4) were assessed using the METAVIR score (*23, 24*). Fibrosis of stage 2 or higher was defined as significant fibrosis and was used as one of the endpoints in this study. A stage score of 2 was considered easily separable from stage 1 as a dividing point, as stage 1 involves fibrosis confined to the portal tract.

Prognostic Factors for Patient Survival and HCV Recurrence

A total of 18 variables potentially associated with patient survival and HCV recurrence were evaluated. Pretransplantation variables included: recipient age; recipient gender; Child-Pugh grade; MELD score; presence of HCC; HCV genotype (1b vs. non-1b); HCV viral load; and history of previous antiviral treatment with interferon. Donor-related variables comprised: age; gender; relation to the recipient (related vs. unrelated); ABO-blood type and HLA compatibilities; graft-to-recipient body weight ratio (GRWR: $<1.0\%$ vs. $\geq 1.0\%$). Posttransplant variables were: induction immunotherapy (tacrolimus vs. cyclosporine, with or without steroid); and administration of steroid boluses.

Statistical Analysis

Overall survival, time to reach fibrosis of stage 2 or more according to liver biopsy (with time to last biopsy for all patients who did not reach fibrosis of stage 2), and time to severe HCV recurrence were evaluated. Severe HCV recurrence was defined as the presence of liver cirrhosis (F4) in a liver biopsy and/or the development of clinical decompensation secondary to liver diseases with portal hypertension (*11*). Cumulative probability curves of survival or HCV recurrence were calculated using the Kaplan-Meier method, and differences between these curves were compared using the log-rank test. The cutoff chosen for quantitative variables was the median, unless stated otherwise. Any variable identified as significant ($P<0.05$) in univariate analysis by log-rank testing was considered a candidate for multivariate analysis using Cox's proportional hazards regression model. Values of $P<0.05$ were considered statistically significant.

RESULTS

Patient Survival

As of the end of May 2005, 65 patients were still alive. One patient had received re-LDLT for graft cirrhosis due to HCV recurrence 31 months after first LDLT and has survived 14 months since then. Causes of death for the 26 patients were: sepsis (n=11); peritonitis (n=4); pneumonia (n=3); recurrent HCC (n=4); chronic rejection (n=2); veno-occlusive disease (n=1); and recurrent HCV (fibrosing cholestatic hepatitis (FCH), n=1). Overall patient survival rate at 5 years was 69%, similar to that of 209 non-HCV patients (71%) who underwent right-lobe LDLT at our institute between February 1998 and June 2004 (PBC/PSC, n=56; HBV cirrhosis, n=53; fulminant hepatitis, n=38; cholestatic disease, n=19; and others, n=43; Fig. 1). Among HCV-positive patients, 5-year survival rate tended to be better in patients without HCC (n=34) than in patients with HCC (n=57), although no significant difference was identified (82% vs. 60%, $P=0.069$; Fig. 2). None of the variables listed above as prognostic factors for patient survival and HCV recurrence displayed any significantly associations with patient survival.

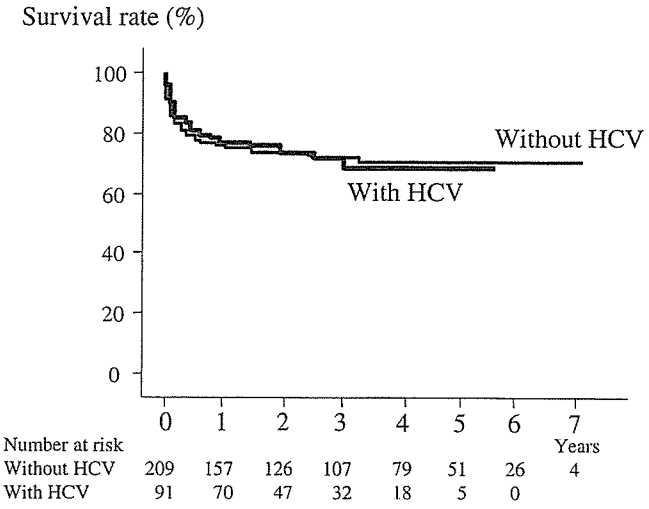

FIGURE 1. Patient survival after living donor liver transplantation (HCV vs. non-HCV). Overall patient survival rate for HCV-positive patients was 69% at 5 years, similar to that for non-HCV patients (71%, n=209) who underwent right-lobe LDLT at our institute between February 1998 and June 2004.

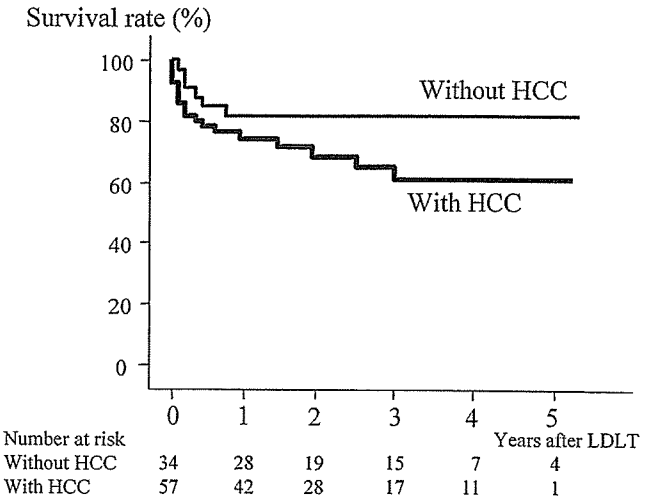

FIGURE 2. Patient survival for HCV patients (with vs. without HCC). Among HCV-positive patients, survival rate tended to be better for patients without HCC (n=34) than for patients with HCC (n=57), although no significant difference was found (82% vs. 60%, $P=0.069$).

Evaluation of Liver Histology

During the first year after LDLT, necroinflammatory changes suggesting recurrent hepatitis C were observed in 50 patients: A1 in 32 patients; A2 in 17 patients; and A3 in one patient. Afterwards, the percentage of patients who received biopsy among those alive at yearly intervals was as follows: 1 year, 86% (60/70); 2 years, 72% (34/47); 3 years, 44% (14/32); 4 years, 33% (6/18); and 5 years, 20% (1/5). Ten patients who were alive for >1 year (range, 22–72 months) without any

evidence of progressive liver disease never underwent any biopsy at 1 year or later. Significant fibrosis (stage 2 or more) was identified in 23 patients, including 3 patients who developed to fibrosis of stage 4 within 1 year. Excluding 19 patients who died within 1 year without identified fibrosis and the 10 patients alive without biopsy for >1 year, cumulative probability of significant fibrosis was 19% at 1 year after LDLT, 39% at 2 years, and 58% at 3 years. Follow-up was censored at the time of last biopsy for all patients who did not reach fibrosis of stage 2.

The results from univariate analysis of risk factors for significant fibrosis are summarized in Table 2. Female recipient and male donor were significantly associated with development of significant fibrosis. Analysis of quantitative variables, donor age and GRWR, demonstrated that rate of significant fibrosis was not significantly different even when cutoff levels were changed. Multivariate analysis with Cox's hazards model showed that neither female recipient nor male donor represented independent risk factors for significant fibrosis (data not shown).

Severe Recurrence of HCV

FCH was diagnosed in two patients, one of whom died of liver failure 7 months after LDLT. The other patient suffered from FCH 2 months after LDLT, but recovered from cholestasis and was still alive after 28 months. Final liver biopsies of both patients showed fibrosis of stage 4. Another three patients also developed fibrosis of stage 4 during follow-up. One patient whose liver biopsy led to a diagnosis of recurring chronic hepatitis with F3 fibrosis 10 month after LDLT also suffered from stenosis of duct-to-duct biliary anastomosis. This patient underwent hepaticojejunostomy, but died of fungal pneumonia 1 month later. Liver histology at autopsy revealed F4 fibrosis. Another patient received re-LDLT for recurrent decompensated cirrhosis, as described above. The other patient who developed to biopsy-proven stage 4 fibrosis at 50 months was alive without decompensation as of 63 months after LDLT. In total, severe recurrence (progression of biopsy-proven cirrhosis and/or occurrence of clinical decompensastion) was diagnosed in five patients, and cumulative probability of severe recurrence was 8% at 2 years. Of the five patients presenting with severe recurrence, three were female and all had received the liver graft from a male donor.

TABLE 2. Risk factors associated with fibrosis of stage 2 or higher

Factors	n	Recurrence rate (number of patients at risk) 1 year	2 years	3 years	*P* value
Total[a]	62	19% (50)	39% (14)	58% (5)	
Recipient sex					0.006
Male	40	10% (36)	27% (10)	48% (4)	
Female	22	36% (14)	60% (4)	70% (1)	
Donor sex					0.047
Male	36	25% (28)	49% (6)	59% (1)	
Female	26	12% (22)	26% (8)	47% (4)	

[a] The 19 patients who died within 1 year without identified fibrosis and the 10 patients alive without biopsy for >1 year were excluded.

DISCUSSION

In the present study, only one patient had died of recurrent HCV as of the time of writing, and the majority of posttransplant deaths were attributable to postoperative complications occurring within a few months after LDLT. Infectious complications such as sepsis, pneumonia and peritonitis represented the most common causes of early mortality, as was the case in HCV-negative recipients. One-year mortality rates were 23% and 25%, respectively. Currently, overall 5-year patient survival rate for HCV-positive patients appears similar to that for non-HCV patients in our adult LDLT series (69% vs. 71%; Fig. 1). Of the 91 patients, HCC was present in 57 (63%), including 25 patients who exceeded the Milan criteria. Four patients died of recurrent HCC after LDLT, and the survival rate tended to be lower for patients with HCC than for patients without HCC (82% vs. 74% at 1 year, and 82% vs. 60% at 5 years; Fig. 2). Only one patient in this cohort had to undergo re-transplantation, and 5-year graft survival rates were 68% for all patients and 82% for patients without HCC. These results are comparable to the reported DDLT outcomes in the UNOS database: patient and graft survival rates of HCV-positive patients (n=3955) at 2 years were 81% and 75%, respectively (*13*); and rates for HCV-positive but HCC-negative patients (n=5640) at 5 years were 74.6% and 69.9%, respectively (*7*).

Progression of fibrosis due to recurrent chronic hepatitis is key to determining graft prognosis after liver transplantation for HCV-positive recipients. In the present study, progression of fibrosis in the liver biopsy was assessed and fibrosis to stage 2 or more was defined as significant fibrosis. The probability of progression to significant fibrosis was 39% at 2 years after LDLT. Several risk factors associated with posttransplant recurrence of hepatitis C have been identified (*5, 25–27*). These include pretransplant viral load, genotype 1b, donor age and graft steatosis, recipient age, race, gender, coexistence of HCC, and rejection treatment using bolus steroid or antilymphocyte preparations. Among the 18 potential variables examined in our study, univariate analysis identified female recipient and male donor as closely related to significant fibrosis. However, multivariate analysis showed that neither variable represented a significant independent risk factors. Actually, some correlation among these two variables was noted. Of the 30 female recipients, 24 had received a liver graft from a male donor (son or husband). An association between female gender of the recipient and severity of recurrent HCV has been demonstrated in previous studies (*6, 7*). However, no previous reports have implicated gender of the donor as an involved factor. Although difficulty exists in determining which is the predominant factor, the combination of male donor and female recipient may exert a negative impact on HCV recurrence.

Rapid proliferation of hepatocytes during postoperative graft regeneration may contribute to a higher rates of both HCV replication and severe recurrence in LDLT (*11*). This seems to imply a higher risk of recurrence in cases involving smaller grafts, which are supposed to undergo regeneration at a higher rate. Our study, however, showed that progression of significant fibrosis was similar for patients who received grafts with GRWRs of <1.0% or ≥1.0%. This result is supported by a recent report (*28*) showing that liver

regeneration following partial liver transplant does not increase the risk of HCV recurrence. Likewise, neither the relationship between donor and recipient nor degree of HLA matching seemed to influence recurrence. The results of our study thus do not support the hypothesis that these factors may exert negative effects on HCV recurrence in LDLT patients.

Due to the small number of patients treated using DDLT in Japan, HCV recurrence rates could not be compared between DDLT and LDLT. In previous studies on HCV recurrence after DDLT (*1, 13, 25, 29, 30*), histologically diagnosed recurrence of chronic HCV occurred in 65–90% of HCV-positive DDLT recipients during the first 2 years. However, a lack of uniform definitions for recurrent HCV, even when histological liver biopsy findings are used as criteria, has been indicated as one reason for the difficulties in comparing studies on HCV recurrence (*31*). Recently, a report from Spain demonstrated that severe recurrence of hepatitis C, defined as the development of cirrhosis or clinically decompensated liver disease, is more frequent in LDLT recipients (*11*). According to this report, the 2-year probability of developing severe recurrence was 45% after LDLT, compared to 22% after DDLT ($P=0.019$). When the same definitions were applied, rate of severe recurrence was only 8% at 2 years in our study. Arguably as many as 19 patients (21%) died within 1 year before developing HCV recurrence in our series. However, considering that the probability of either death or severe recurrence was 29% at 2 years, the results for our LDLT series were not likely to be greatly inferior to other reported cases.

In conclusion, postoperative patient survival was similar for HCV-positive and -negative recipients in our adult LDLT series. Rate of recurrence for chronic HCV and prevalence of progression to severe disease for our LDLT recipients appeared comparable to those for DDLT reported in the literature. Although these results need to be confirmed with a longer follow-up period, the present findings suggest that LDLT can produce acceptable outcomes for patients suffering from end-stage liver disease due to chronic HCV.

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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.

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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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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

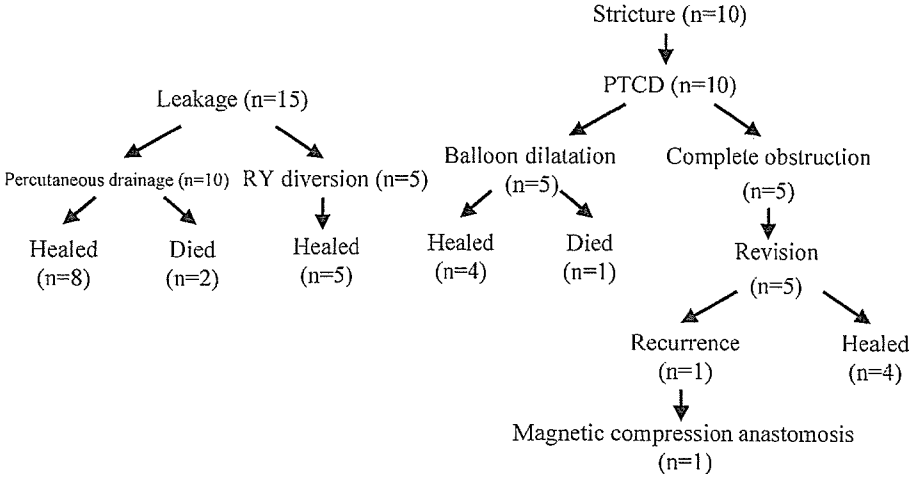

FIGURE 1. Summary of clinical outcome after biliary complications in Roux-en-Y choledochojejunostomy. PTCD, percutaneous transhepatic cholangiography and drainage.

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

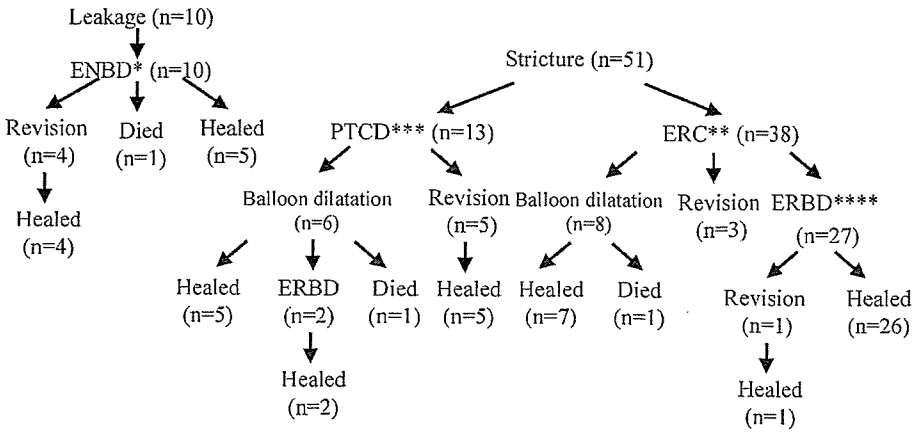

FIGURE 2. Summary of clinical outcome after biliary complications in duct-to-duct choledochocholedochostomy. ENBD, endoscopic nasobiliary drainage; ERC, endoscopic retrograde cholangiography; PTCD, percutaneous transhepatic cholangiography and drainage; ERBD, endoscopic retrograde biliary drainage.

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]

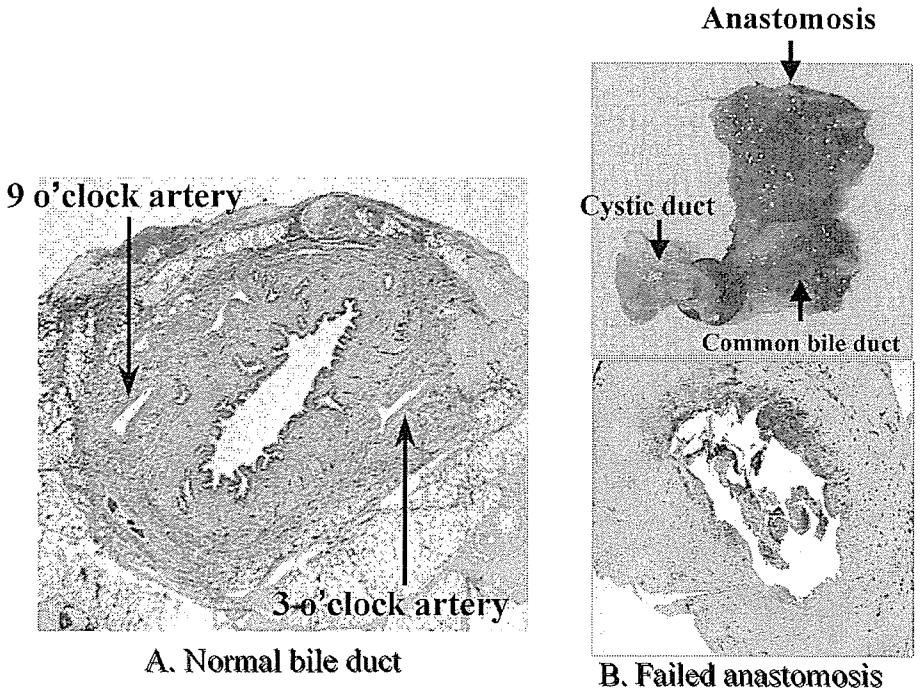

FIGURE 3. Histologic examination of the failed duct-to-duct choledocho-choledochostomy often shows the loss of the 3 and 9 o'clock arteries on the recipient side. Preservation of periductal microcirculation on the recipient side is a key factor for successful anastomosis. A, Normal common bile duct with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