Table 3. Reported series of liver transplantation for patients with HIV infection

First author, year, institution (Journal[Ref.])		*n*	Survival	Findings
Ragni, 2003, Pittsburgh (J Infect Dis[27])	HIV only	24	3-Year 72.8%	Risk factor for mortality after LT
	HIV+HCV	15	3-Year 56.9%	CD4+ <200/μl, HAART resume not possible HIV viral load >400 copies/ml
Neff, 2003, Pittsburgh (Liver Transpl[28])	HIV positive	16	14/16	2 HAART discontinued due to liver damage 13/16 HIV negative before LT CD4+ <200/μl (6/16), <100/μl (2/16) ACR (6/16). FK trough level increased (6/16)
Fung, 2004, Review	HIV positive (total)	51	80%	68% HCV coinfection, 26% hemophilia
(Liver Transpl[25])	(Pittsburgh)	29	20/29	
Norris, 2004, London (Liver Transpl[29])	HIV+HCV	7	2/7	4 HCV recurrence, died with sepsis
	HIV only	7	7/7	HBV no recurrence
Moreno, 2005, Madrid (Liver Transpl[30])	HIV+HCV	4	3/4	1 died with FCH 17 months after LT CD4+ <100/μl (2/16) ACR (1/4), no opportunistic infection
Radecke, 2005, Essen (Liver Int[31])	HIV+HCV	5	2/5	2 survived case on HAART
Miró, 2007, Barcelona (J HIV Ther[11])	HIV+HCV	Review ($n > 200$)	1-Year 50%–55% (without LT)	Indication for LT: CD4+ >100/μl, HIV negative SVR rate (post LT) 15%–20%
Schreibman, 2007, Miami (Transplantation[20])	HIV positive	15	3-Year 73.3%	Infectious complication 26.7% vs 8.7% ($P = 0.006$)
	HIV negative	857	3-Year 79.4%	Indication for LT: CD4+ >100/μl, HIV <200 copies/mm^3
Reiberger, 2008, Vienna (Eur J Clin Invest[32])	HIV+HCV (post)	31		HCV viral load increased on immunosuppression
	HIV+HCV (pre)	20		IFN effective if CD4+ preserved
	HCV only (pre) HIV+HCV (post LT) 50%, HCV only (post LT) 56%	25		SVR rate: HIV–HCV (post LT) 28%
Mindikoglu, 2008, UNOS (Transplantation[26])	HIV positive	138	2-Year 70%, 3-year 66%	All after HAART era, HCV+ poor prognostic factor
	HIV+HCV	58	2-Year 52%	
	HIV negative	520	2-Year 81%, 3-year 77%	
Duclos-Vallée, 2008, France (THEVIC study group)	HIV+HCV	35	2-Year 73%, 5-year 51%	Pre LT MELD score most important factor for mortality
(Hepatology[21])	HCV only	44	2-Year 91%, 5-year 81%	HIV coinfection: fibrosis progression (>F2) quicker LT indication: CD4+ > 100/μl, HIV negative
Samri, 2009, France (multicenter) (J Hepatol[33])	HIV+HCV	14	2-Year 93%	LT indication: HIV negative, no AIDS FK and HAART resumed 2 weeks after LT, FK overdose 5/14 (36%) 1 FCH died. 1-year F2 2, F3 1, F4 (FCH) 2
Testillano, 2009, Bilbao (Transplant Proc[34])	HIV+HCV	12	3-Year 62%	Patient survival, HCV recurrence, FCH not different ($P = 0.09$) from LT for patients without HIV
	HCV only	59	3-Year 84%	

.HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; HAART, highly active antiretroviral therapy; FCH, fibrosing cholestatic hepatitis; LT, liver transplantation; ACR, acute cellular rejection; SVR, sustained virological response; IFN, interferon; UNOS, United Network for Organ Sharing; MELD, model for end-stage liver disease; FK, tacrolimus

drugs.[42–45] The best time to start interferon treatment and other post-transplantation measures to prevent HCV, optimal immunosuppressive regimens, and ways of monitoring drug blood levels are being studied, and further reports are expected.[46–51]

According to a review on the effects of interferon treatment after liver transplantation, the SVR rate ranges from 0% to 50%. This article reported that there had been many side effects in HIV-positive patients, especially caused by anemia and a low white blood cell

count, and that the continuation of treatment for such patients had been made possible by administration of the growth factor.[52]

Some Studies Refer to the Correlation Between T-Cell Counts and Acute Rejection

In practice, some studies showed the rate of acute cellular rejection to be similar, regardless of HIV positivity.[11,53] Induction therapy without steroids has also been attempted,[54] and the rate of opportunistic infection is reported to be similar after organ transplantation in HIV-positive patients.[20] Thus, the number of CD4+ lymphocytes present prior to liver transplantation is an important factor.

HAART Drugs Can Cause Hepatic Toxicity[55]

If HAART drugs induce liver failure, the best HAART drug to use after liver transplantation must be selected carefully. HAART drug toxicity can also induce complications with acute cellular rejection or other hepatic problems after liver transplantation. A liver biopsy may be needed to elucidate the real cause. Noncirrhotic portal hypertension has recently been reported in HIV-positive patients. HAART drugs may be related to those unresolved pathogeneses.[56]

The Control of Infection After Liver Transplantation for HIV–HCV Coinfection Is Based on the Count of CD4+ lymphocytes Obtained During the Perioperative Period

Therefore, the timing of recommencement of the HAART drug and the preoperative CD4+ lymphocytes counts are both important factors. According to previous reports, prophylaxis against bacterial and viral infections seems to be the same as for liver transplantation without HIV infection.[20]

The Presence of Hemophilia Makes It Difficult to Manage the Coagulation Time and Control Bleeding During the Intra- and Postoperative Period Before a Transplanted Liver Starts to Function

Moreover, when considering LDLT and when only carrier-donors exist, an assessment of the risks associated with the resection of the carrier-donor's liver would also be a problem.[37]

Conclusions

This review is an overview of liver transplantation performed to date for HIV–HCV coinfected persons. Although there have been no cadaveric liver transplantations for these patients in Japan,[57] conventional knowledge about cadaveric liver transplantation may be applicable in most cases, despite the unresolved problems. In light of the fact that most of these Japanese patients are the victims of contaminated blood products, we believe that the number of liver transplantations will increase, in the context of medical relief.[58]

Acknowledgment. This work was supported in part by a Grant-in-Aid for Research on HIV/AIDS from the Ministry of Health, Labour and Welfare of Japan.

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Surg Today (2011) 41:1026–1028
DOI 10.1007/s00595-010-4376-z

SURGERY TODAY

How to Do It

Living Donor Liver Transplantation with Extensive Caval Thrombectomy for Acute-on-Chronic Budd–Chiari Syndrome

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Abstract
The key consideration when performing living donor liver transplantation (LDLT) in patients with Budd–Chiari syndrome (BCS) is careful management of a stenotic or occluded inferior vena cava (IVC), because it is not possible to replace the recipient stenotic or occluded IVC with donor IVC as in cadaver donor transplantation. We describe how we performed LDLT with extensive thrombectomy in a patient with acute-on-chronic BCS with a totally thrombosed retrohepatic IVC. The operation was successful and the patient remains well, with follow-up images showing a patent IVC and hepatic veins. To our knowledge, LDLT for a BCS patient with severe extensive caval thrombus has never been reported before. We consider that the successful outcome of this patient clearly demonstrates the feasibility of our technique of extensive thrombectomy, without a vessel graft, to manage a stenotic or occluded IVC in LDLT in patients with BCS.

Key words Living donor liver transplantation · Budd–Chiari syndrome · Thrombectomy · Cavoplasty

Introduction

Liver transplantation is ultimately the treatment of choice for patients with Budd–Chiari syndrome (BCS), especially those with fulminant forms of BCS, those with established cirrhosis or frank fibrosis, and those with defined hepatic metabolic defects such as protein C or protein S deficiency.[1] The safety and efficacy of liver transplantation for patients with BCS has been confirmed by a multicenter study conducted in Europe and by a United States national registry analysis.[2,3]

In contrast to deceased donor liver transplantation, when the recipient stenotic or occluded inferior vena cava (IVC) can be replaced with the donor IVC, in living donor liver transplantation (LDLT) it cannot, so appropriate management of a stenotic or occluded IVC is imperative in LDLT in the patient with BCS. We recently performed successful LDLT with extensive thrombectomy in a patient with acute-on-chronic BCS with a totally thrombosed retrohepatic IVC.

Patient

A 63-year-old man was admitted with general fatigue and vomiting to a local hospital, where liver dysfunction was confirmed. He was transferred to our hospital when his liver function deteriorated severely, with the following laboratory findings: serum total bilirubin 5.6 mg/dl, aspartate aminotransaminase 3573 IU/l, and alanine aminotransferase 2034 IU/l. He also had grade 3 hepatic encephalopathy. Abdominal computed tomography (CT) showed occlusion of the middle and left hepatic veins with thrombus in the IVC, extending from below the renal vein to the suprahepatic IVC (Fig. 1), as well as moderate ascites, and a patent portal vein. As a result of intensive care including plasma exchange, the acute liver failure improved and the patient was referred as a candidate for LDLT, with a diagnosis of BCS.

Technique

The patient underwent LDLT 3 months after the onset of acute liver failure. He received a right lobe liver graft from his son. The intraoperative findings revealed a hard and irregular liver, with moderate ascites and signs of portal hypertension.

Reprint requests to: S. Eguchi
Received: August 24, 2009 / Accepted: February 18, 2010

The preoperative abdominal CT showed a thrombosed IVC, so a portovenous bypass was established early in the procedure. The supradiaphragmatic IVC was cross-clamped after opening the pericardium. We introduced a Fogarty catheter through the opened and widened orifice of the right hepatic vein and common trunk of the left and middle hepatic veins. Since part of the thrombus was difficult to remove by using only a Fogarty catheter, we performed thrombectomy through a longitudinally opened IVC wall with segmental cross-clamp.

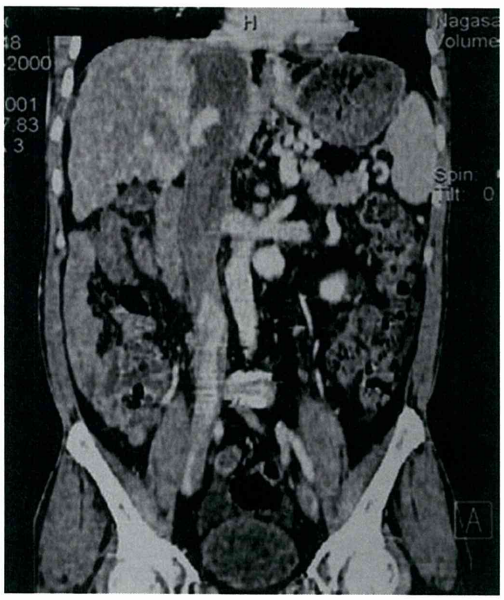

Fig. 1. Coronal view of preoperative abdominal computed tomography (CT) showed thrombosis of the inferior vena cava (IVC) extending from the suprahepatic IVC to below the left renal vein, a cirrhotic liver, and collateral vessels

After removing the thrombus from the IVC, we performed cavoplasty to match the orifice of donor's hepatic vein without any patch or interposition graft. The right hepatic vein of the graft was anastomosed to the recipient's IVC in an end-to-side fashion (Fig. 2), and portal, arterial, and biliary anastomoses were completed in a standard fashion. Immediately after LDLT, intravenous heparin therapy was started, which was later changed to oral warfarin. The patient had an uneventful postoperative recovery and was discharged on postoperative day 28. Follow-up CT confirmed a patent IVC and hepatic veins (Fig. 3). The patient is now doing well without any signs of recurrence of BCS.

Discussion

Yamada et al.[4] reported three cases of patients who underwent LDLT without replacement of a chronically occluded IVC because they had well-developed hemiazygos veins. As our patient did not have well-developed hemiazygos veins, the IVC had to be preserved as a return from the lower half of the body and as an outflow route from the liver.

As options to replace an occluded retrohepatic IVC in LDLT, Yan et al.[5] reported the usefulness of a cryopreserved vena cava graft, and Shimoda et al.[6] advocated an autologous vein graft. Although these

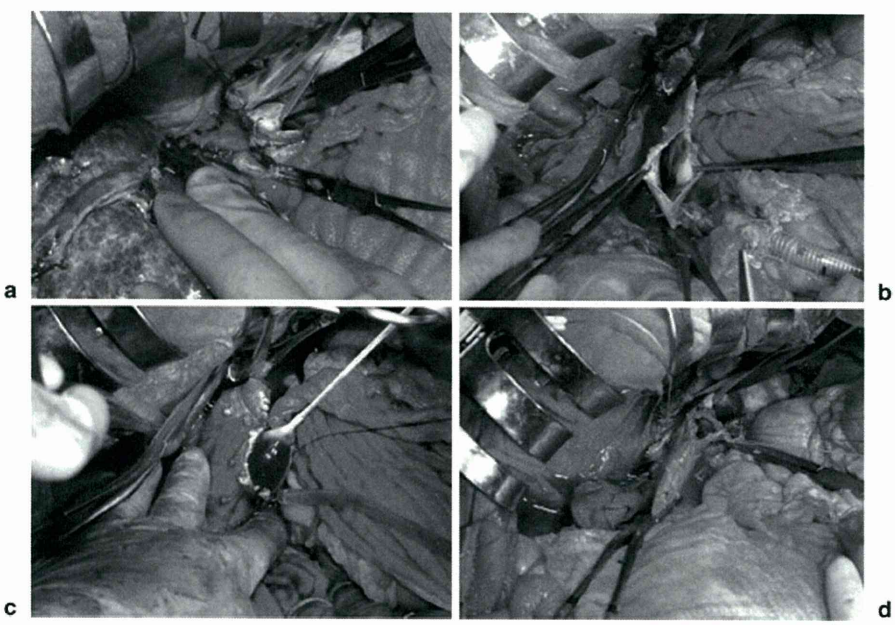

Fig. 2. Intraoperative photos showing cross-clamping of the IVC after opening the pericardium (**a**), opening of the IVC and subsequent thrombectomy with a Fogarty catheter (**b**, **c**), and cavoplasty performed to match the right hepatic vein of the graft (**d**)

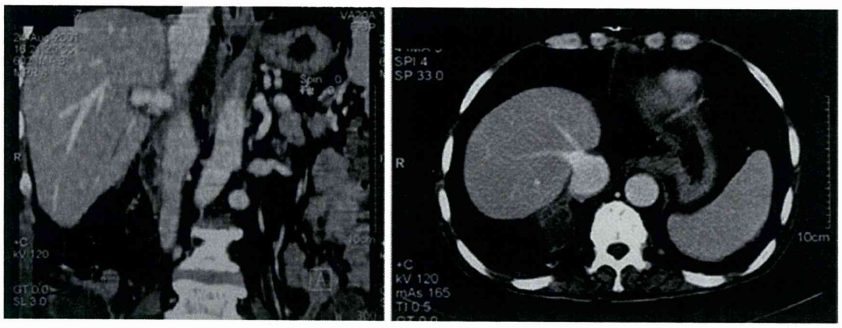

Fig. 3. Follow-up abdominal CT confirmed a patent IVC with no signs of recurrent thrombus

techniques have merit, appropriate cryopreserved grafts or autologous vessel grafts are not always available. Lee et al.[7] described replacing the diseased stenotic retrohepatic vena cava of the recipient with a large-caliber Dacron interposition graft, placed between the right atrium and the infrahepatic IVC. Although long-term outcomes should be evaluated, their technique might be feasible if the thrombotic obstruction of the suprahepatic IVC extends almost to the junction of the right atrium and the intrapericardiac IVC.[7]

The successful outcome of our patient confirms the feasibility of our technique, including extensive thrombectomy without a vessel graft, for managing a stenotic or occluded IVC in LDLT for the BCS patient. In slow-progressing BCS, the wall of inferior caval vein can become fibrotic if thrombosis exists there long term. Although our technique might be applicable for slow-progressing as well as acute BCS, it is important to check if the IVC has a fibrotic wall that could make the IVC stenotic even after thrombectomy.

To the best of our knowledge, this is the first report of LDLT in a BCS patient with such severe extensive caval thrombus. Thus, for patients with acute deteriorating BCS with IVC thrombosis, and for those without CT evidence of a well-developed long-standing hemiazygos vein, we consider LDLT with extensive thrombectomy to be a good treatment option.

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S Eguchi, *et al.*
www.hepato-gastroenterology.org
DOI 10.5754/hge11589
2012; 59(115-116): Ahead of print.

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Is Preservation of Middle Hepatic Vein Tributaries during Right Hemi-Hepatectomy Beneficial for Live Donor Liver Transplantation?

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KEY WORDS: Live donor hepatectomy; Right lobe; Middle hepatic vein; Tributaries; Preservation.

ABBREVIATIONS: Living Donor Liver Transplantation (LDLT); Middle Hepatic Vein (MHV).

ABSTRACT

Background/Aims: When right hemi-hepatectomy without middle hepatic vein (MHV) is performed in a living donor (LD), MHV tributaries such as V5 and V8 may be preserved during parenchymal transection to preserve liver function and reduce the damage of the graft. However, no study has so far investigated whether this preservation of MHV tributaries during parenchymal transection has impact on live donor operation or graft function. **Methodology:** Of 52 hepatectomies for right lobe LD, MHV tributaries were preserved during hepatic parenchymal transection in 11 cases, while, in the remaining 41 cases MHV tributaries were sacrificed when those were encountered during hepatic parenchymal transection. **Results:** There was no significant difference in blood loss, operative time, zenith liver enzyme level in a donor and rate of graft failure in a recipient. **Conclusions:** It was demonstrated that there was no significant effect of outflow preservation from MHV tributaries on LD hepatectomy for right lobe donation and subsequent liver transplantation.

INTRODUCTION

The method for hemi-hepatectomy in a living donor is technically different from that carried out for hepatic tumors. Usually, when right lobe is resected without middle hepatic vein (MHV) for hepatic tumor, drainage veins such as V5 or V8 from anterior sector of right lobe to MHV are ligated and transected during parenchymal transection (1,2). However, when right hemi-hepatectomy is performed in a living donor, V5 and V8 may be preserved during parenchymal transection to preserve liver function and reduce the damage of the graft due to congestion of anterior sector of right lobe graft. This preservation of V5 and V8 during parenchymal transection in a living donor may increase blood loss because it is technically cumbersome to divide hepatic parenchyma with V5 and/or V8 still in place. However, no study has so far investigated this point.

METHODOLOGY

Patients

Eleven of 52 hepatectomies for right lobe living donor were performed with V5 or V8 preservation during hepatic parenchymal transection (preserved group, n=11, **Figure 1**). They were transected right before graft explantation. On the other hand, in the remaining 41 cases V5 and/or V8 was sacrificed when those were encountered during hepatic parenchymal transection (sacrificed group, n=41). Whether V8 and/or V5 in a donor should be preserved and should be reconstructed in a recipient was determined according to a previously reported method (3).

Methods

Method for hepatic parenchymal transection was reported elsewhere previously (4).

Occlusion of the hepatic arterial and portal inflow was not used in any case. During parenchymal division, upward traction on the tape hanging maneuver leads to follow the direct plane and facilitates the exposure and homeostasis of the deeper parenchymal plane in front of the IVC (5).

All data are expressed as median values with ranges. The statistical analysis was performed using the Mann-Whitney U-test for continuous values. A statistical difference was defined as a *p*-value of less than 0.05.

RESULTS

The resected liver volume was comparable between the groups (**Table 1**). The amount of blood loss during operation was not different between the two groups (preserved group *vs.* sacrificed group: median 1000g *vs.* 697g (p=0.077). The operation time seemed to be prolonged in the preserved group than that in the sacrificed group. (486min *vs.* 423min, p=0.053). In addition, donor liver function after partial liver donation was same after the operation. The rate of graft failure in both groups was the same in the two groups. In the preserved group all V5 and/or V8 veins were reconstructed in the recipients whereas only 2 reconstructions were performed in the sacrificed group based on the previous report (3).

DISCUSSION

The present study demonstrated that there was no significant effect of outflow preservation from V8 and V5 on living donor hepatectomy for right lobe donation and subsequent liver transplantation. Therefore, there was no advantage to preserve V5 and/or V8 until the end of partial liver graft harvesting in a living donor for both donor

and recipient in this series. Even operative time for donor hepatectomy tended to be longer in the preservation than that in divided group. Therefore, if recipient's operation is being performed as scheduled V5 and/or V8 could be sacrificed during parenchymal transection in a living donor right lobe hepatectomy without MHV.

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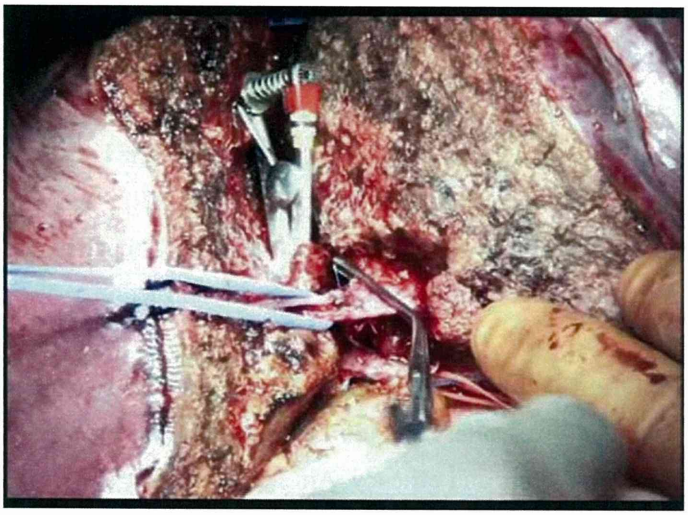

FIGURE 1. In the preserved group V5 and/or V8 were preserved until graft removal.

TABLE 1

	Preserved group (n=11)	Sacrificed group (n=41)	*p*
Age	33 (22-53)	45 (20-67)	0.2
Gender	5:6	19:21	0.62
Resected liver volume (%)	55.4	55.0	0.92
Blood loss (g)	1,000 (460-2,200)	697(130-2,550)	0.078
Operation Time (minutes)	486 (251-633)	423 (297-636)	0.053
Zenith ALT in donors (IU/L)	320 (69-651)	297 (169-1,237)	0.38
Zenith T Bil in donors (mg/dL)	2.3 (0.7-4.2)	2.4 (1.1-5.8)	0.61
V5 and/or V8 reconstruction in recipients	11 (100%)	2 (4.9%)	<0.0001
In hospital recipient's death	1 (infection 1)	5 (infection 2 severe rejection 2 hepatic artery thrombus 1)	0.77

Surgical Technique

Elective living donor liver transplantation by hybrid hand-assisted laparoscopic surgery and short upper midline laparotomy

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Background. *Although the technique of liver transplantation is well developed, the invasiveness of the operation can be decreased with laparoscopic procedures.*
Methods. *We performed elective living donor liver transplantation (LDLT) through a short midline incision combined with hand-assisted laparoscopic surgery (HALS). Nine selected patients with end stage liver disease underwent the procedure between July, 2010 and February, 2011 (median age 60, median Child-Pugh 9, median MELD score 14). Splenectomy was performed simultaneously in 7 cases. The liver (and spleen) were mobilized by a sealing device under a HALS procedure with an 8-cm upper midline incision, followed by explantation of the diseased liver (and spleen) through the upper midline incision which was extended to 12 to 15 cm. Partial liver grafts were implanted through the upper midline incision.*
Results. *The median duration of the operation was 741 minutes, the median time needed for anastomosis was 48 minutes, the median blood loss was 3,940 g, and the median liver weight was 866 g. Eight recipients are alive and have good graft function. A difficult implantation for one patient required an additional right transverse incision. When compared with 13 recent liver recipients who underwent LDLT with a regular Mercedes-Benz-type incision, no clinically relevant drawbacks of the HALS hybrid procedure were observed.*
Conclusion. *We have shown the feasibility and safety of LDLT performed through a short midline incision without abdominal muscle disruption with the aid of HALS. (Surgery 2011;150:1002-5.)*

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In an attempt to decrease the morbidity and invasiveness associated with liver surgery, several liver transplant teams have developed laparoscopic approaches to hepatectomy for living donors and patients with hepatic malignancies.[1-5] The surgical procedure performed on liver transplant recipients with portal hypertension is considered one of the most difficult abdominal operations because of the existence of collateral vessels. Nevertheless, selected patients have undergone a less invasive procedure with laparoscopic assistance, including patients with portal hypertension who underwent splenectomy.[6] We postulated that an elective liver transplant recipient procedure could be performed through an upper midline laparotomy after mobilization of the liver and spleen using hand-assisted laparoscopic surgery (HALS). We report a safe method for less invasive liver transplantation via a short midline incision without disruption of the abdominal musculature and nerves.[7]

Accepted for publication June 15, 2011.

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0039-6060/$ - see front matter

doi:10.1016/j.surg.2011.06.021

MATERIALS AND METHODS

Living donor liver transplantation (LDLT) through a midline incision using a hand-assisted laparoscopic procedure was planned in 9 patients between July 2010 and February 2011. Seven patients had liver cirrhosis due to hepatitis C, in

Table. Comparison of patient demographics and operative results

	HALS + upper midline (n = *9*)	*Mercedes-Benz-type incision* (n = *13*)	P *value*
Age	60 (44–69)	54 (27–72)	NS
Gender (Male:Female)	4:5	8:5	NS
Child-Pugh score	9 (6–14)	10 (5–15)	NS
MELD score	14 (7–43)	15 (7–35)	NS
Graft (RL:ELL)	1:8	6:7	NS
Operation duration (min)	741 (599–839)	812 (654–1,097)	$P < .05$
Anastomosis (min)	48 (37–55)	36 (32–65)	NS
Blood loss (g)	3,940 (1300–18,400)	3,350 (520–5,600)	NS
Explanted liver (g)	866 (596–1,270)	830 (399–1,250)	NS
Outcome	1 death	2 deaths	NS

Values are expressed as median (range).
HALS, Hand-assisted laparoscopic surgery; *MELD,* model for end-stage liver disease; *Anastomosis,* anastomosis for hepatic vein and portal vein reconstruction; *ELL,* extended left lobe graft with middle hepatic vein; *RL,* right lobe graft.

whom splenectomy was performed simultaneously. One patient required LDLT because of hepatitis B cirrhosis, and another for Caroli's disease. The Ethics Committee of Nagasaki University Hospital approved a laparoscopic approach for the living donors as well. After experience with the 3 living donor right hepatectomy procedures, we planned to introduce the procedure in the recipient operation as well. The laparoscopic procedure was described in detail to the recipients and they gave their written consent. Patient demographics are provided in the Table. This combined laparoscopic and upper midline laparotomy procedure was indicated only for elective LDLT without a previous history of upper abdominal surgery. Neither ascites nor the degree of portal hypertension was considered as an exclusion criterion. Splenectomy was performed for preemptive interferon therapy after the liver transplantation.

Operative technique. Patients were placed supine with arms adducted and a urinary catheter, and arterial and central venous lines were inserted. An 8-cm upper midline laparotomy was made followed by a 12-mm infra umbilical incision for the laparoscope. A Gelport (Applied Medical, Rancho Santa Margarita, CA) was used in at the 8-cm incision, and a 5-mm port was placed in the right and left lateral upper abdomen under pneumoperitoneum (CO_2 at 8 mmHg) (Fig, *A*). This configuration enabled the first assistant surgeon, who stood on the left side of the patient, to use the hand port for liver manipulation. The primary operator stood on the right side and used the right lateral 5-mm port for dissection. Using a laparoscopic sealing device (Enseal; Ethicon Endo-Surgery, Cincinnati, OH) and hand assist, the right lobe of the liver was mobilized until the inferior vena cava was exposed (Fig, *B*). For patients who needed splenectomy, the primary operator moved to the left side and used the left lateral 5-mm port to mobilize the spleen from the retroperitoneum, which was handled by the first assistant surgeon through a Gelport from the right side, using a sealing device. After those bilateral mobilizations, the midline incision was extended to 12–15 cm, and a wound protector was applied. The wound was retracted and opened with the Omnitract retractor. Under direct view, the short hepatic veins were divided and the right hepatic vein was encircled through a midline incision as well as by transection of the splenic hilum with an endovascular stapler. After hepatic hilum dissection, explantation of the liver was performed in our regular manner without veno-veno bypass (Fig, *C*).

Implantation of the left hepatic lobe with the middle hepatic vein was performed through the midline under cross-clamping on inferior vena cava using the standard procedure, followed by arterial and biliary reconstruction. Implantation of the right hepatic lobe was performed under partial clamping on inferior vena cava. After the procedure (Fig, *D*), 2 drains were placed through the 5-mm trochers, and the midline wound was closed.

In order to clarify the effect of our HALS hybrid procedure, data from 13 recent cases of the LDLT procedure involving a Mercedes-Benz-type incision after January 2010 were analyzed and compared (Table).

Statistical analysis. Univariate analysis was performed using the chi-square test for categorical factors and the Mann-Whitney test for numerical values. *P* values of less than .05 were considered to be statistically significant.

RESULTS

The Table shows the patient demographics and operation results for our hybrid procedure of LDLT in comparison with LDLT under regular Mercedes-Benz-type incision. Case 2 had massive

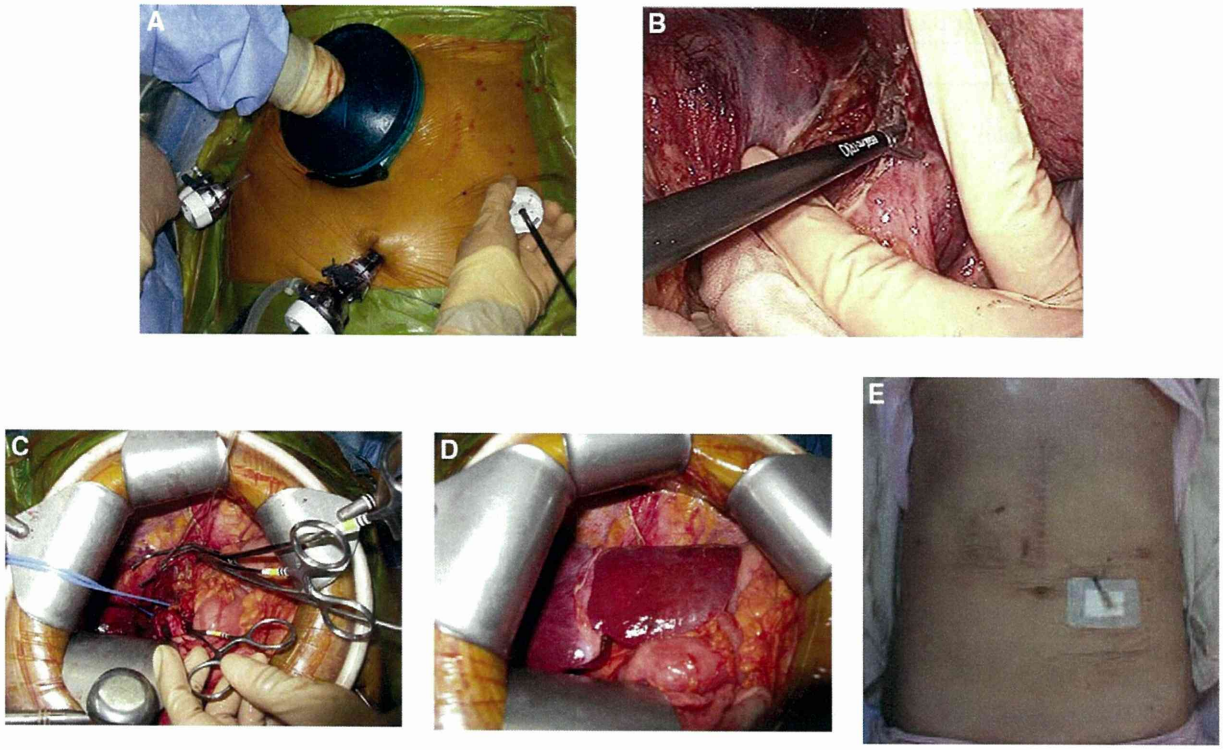

Fig. Case 2, 68 years old, female. (*A*) Hand-assisted port was applied for pneumoperitoneum. (*B*) Laparoscopic mobilization of the diseased liver. (*C*) Anhepatic phase though midline incision. (*D*) Implanted extended left liver lobe graft. (*E*) The abdominal wound 2 months after the operation. A biliary splint and tube jejunostomy was still placed and covered with white gauze.

3.5-L ascites that was evacuated through the laparotomy. A left lobe graft with the middle hepatic vein was implanted through the upper midline incision in 8 patients. The median duration of the operation was 741 minutes (range, 599–839) with a median blood loss of 3,940 ml (range, 1,300–18,400). The hepatic venous and portal venous reconstruction lasted a median of 48 minutes (range, 35–55). In case 2, the caudate lobe vein was also reconstructed. One case (Case 8) required an additional right transverse incision as it involved a difficult implantation. Eight recipients are alive and have excellent graft function. One death (Case 8) occurred due to thrombolytic microangiopathy on day 68. The wound in Case 2 was shown at 2 months after the LDLT (Fig, *E*).

When the results of the HALS hybrid procedure were compared with those of 13 recent LDLT recipients performed using a regular Mercedes-Benz-type incision, no clinically important limitations were observed with the HALS hybrid procedure (Table). In fact, the operative time was less in HALS hybrid cases (HALS: median 741 vs Mercedes-Benz: 812 minutes). Otherwise, there were no important differences between HALS hybrid cases and regular incision cases.

DISCUSSION

We showed the feasibility of LDLT through a midline incision without abdominal muscle disruption as occurs with the usual transverse incision combined with HALS. Because LDLT is performed usually in an elective manner, this procedure could be planned and prepared for.

Before this study, we had performed 130 LDLTs through the usual transverse Mercedes-Benz-type incisions.[8] Based on that experience, we presumed that it would be possible to perform explantation of the liver and spleen followed by implantation of the partial graft liver through a midline incision, because the liver hilum and inferior vena cava are usually located in the center of the upper abdomen. Also, because HALS has been used in the hepatectomy from the living donors, hepatic malignancy, and splenectomy, its use in the recipients seemed logical, because the magnified view under laparoscopy would allow us to obtain hemostasis using sealing devices.[9,10] Because the transverse incision is usually needed only for mobilization of the right liver lobe and spleen, the laparoscopic procedure would allow this mobilization, especially in patients with an increased body mass index.[11,12]

During liver transplantation for patients with hepatitis C, we perform splenectomy for postoperative interferon treatment with ribavirin, which is sometimes complicated by thrombocytepenia.[13] For this combined procedure with mobilization of the liver and spleen, as presented in 7 cases, the HALS procedure showed a marked benefit of visualization not possible with the usual open laparotomy. It made sense for us to perform the mobilization of the liver and spleen using HALS under the laparoscope, because after these procedures the liver transplantation could be performed through the short upper midline incision. Quick celiotomy and closure of the abdomen were also benefits of the upper midline incision.[14] Because no muscle disruption occurred, we believe that postoperative rehabilitation was facilitated. The additional duration of the laparoscopic procedure was offset by the rapid opening and closing of the abdominal incision.

In our series, for the hybrid procedure of HALS and a short midline laparotomy, we selected patients without a history of previous upper abdominal surgery. Although there was still a risk of massive bleeding from collateral vessels, the use of a sealing device with a magnified view allowed us to perform the laparoscopic mobilization. The median blood loss during LDLT was similar to what is reported in large LDLT series.[15] Although we have not had serious complications during the procedure, we would not hesitate to add a wide transverse incision if any difficulty occurred during the procedure, as occurred in our case 8.

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Defective human T-lymphotropic virus Type 1 provirus in asymptomatic carriers

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Few studies have specifically examined defective provirus in asymptomatic human T-lymphotropic virus Type 1 (HTLV-1) carriers and its relation to proviral DNA loads (PVLs). To assess the significance of defective provirus in asymptomatic carriers, we examined PVLs in peripheral blood mononuclear cells of 208 asymptomatic HTLV-1 carriers. The mean PVLs determined using primers for the *pol* region were less than that for the *pX* region in these carriers. Analysis of seven carriers with high PVLs for the *pX* region but lower PVLs for the *pol* region showed that four had single nucleotide polymorphisms of proviral genomes for the *pol* region and three had HTLV-1-infected cells with defective provirus. Three carriers with defective provirus showed high PVLs at their initial screens, and PVLs increased after a 10- to 12-year interval in two carriers. Southern blot assay showed clonal expansion of HTLV-1-infected cells, and the predominant clones changed during the observation period. These data suggest that although HTLV-1-infected cells with defective provirus may have a growth advantage, the predominant clones of HTLV-1-infected cells do not always survive for many years in asymptomatic carriers.

Human T-lymphotropic virus Type 1 (HTLV-1) is the causative agent of adult T-cell leukemia/lymphoma (ATL) and a progressive neurological disease known as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP).[1–4] When an individual is infected by HTLV-1, the virus randomly integrates into the genome of affected T-cells in the form of a provirus.[5] The majority of HTLV-1 carriers are asymptomatic, and only a fraction of the number of carriers develops ATL after a long latent period.[6,7] It is thought that HTLV-1 infection drives the proliferation of T-cells, leading to the clonal expansion of HTLV-1-infected cells.[8–11] A high level of HTLV-1-infected cells is considered a risk factor for developing ATL.[12]

The complete HTLV-1 provirus is ~9 kb and contains the coding regions for core protein (*gag*), protease (*pro*), polymerase (*pol*), envelope protein (*env*), regulatory proteins, such as Tax and Rex, and some accessory molecules between 5′ and 3′ long-terminal repeats (LTRs).[5,13] It has been reported that defective provirus was detectable in approximately half of patients with ATL.[14–18] Tamiya *et al.* reported two types of genome deletion in defective provirus.[16] One form (*i.e.*, Type 1) retains both LTRs and lacks internal sequences, such as the *gag* and *pol* regions. The other form (*i.e.*, Type 2) has only the 3′ LTR, and the 5′ LTR and its flanking internal sequences are preferentially deleted. HTLV-1-infected cells harboring Type 2 defective virus were frequently found in patients with ATL.[18] Defective provirus has also been reported to be detectable in asymptomatic HTLV-1 carriers. Morozov *et al.* reported that defective provirus, which lacked large internal sequences, was detectable in 18 of 20 HTLV-1 carriers.[19] However, it has not yet been determined whether the HTLV-1-infected cells with defective provirus are maintained for a long time in asymptomatic carriers and whether the defective provirus is associated with the development of ATL.

In our study, to clarify the significance of defective provirus in asymptomatic carriers, the peripheral mononuclear cells (PBMCs) of 208 HTLV-1 carriers were screened for the presence of defective provirus. Long polymerase chain reaction (PCR) and Southern blot analysis were performed to determine the changes in clonality of HTLV-1-infected cells

Key words: HTLV-1, asymptomatic carrier, proviral DNA loads
Abbreviations: ATL: adult T-cell leukemia/lymphoma; CTL: cytotoxic T-lymphocytes; HBZ: HTLV-1 basic leucine zipper factor; HTLV-1: human T-lymphotropic virus Type 1; LTR: long-terminal repeat; PBMCs: peripheral mononuclear cells; PCR: polymerase chain reaction; PVLs: proviral DNA loads
Grant sponsors: Ministry of Education, Science, Sports and Culture, Japan, Miyazaki Prefecture Collaboration of Regional Entities for the Advancement of Technological Excellence, JST
DOI: 10.1002/ijc.25450
History: Received 29 Jan 2010; Accepted 28 Apr 2010; Online 12 May 2010
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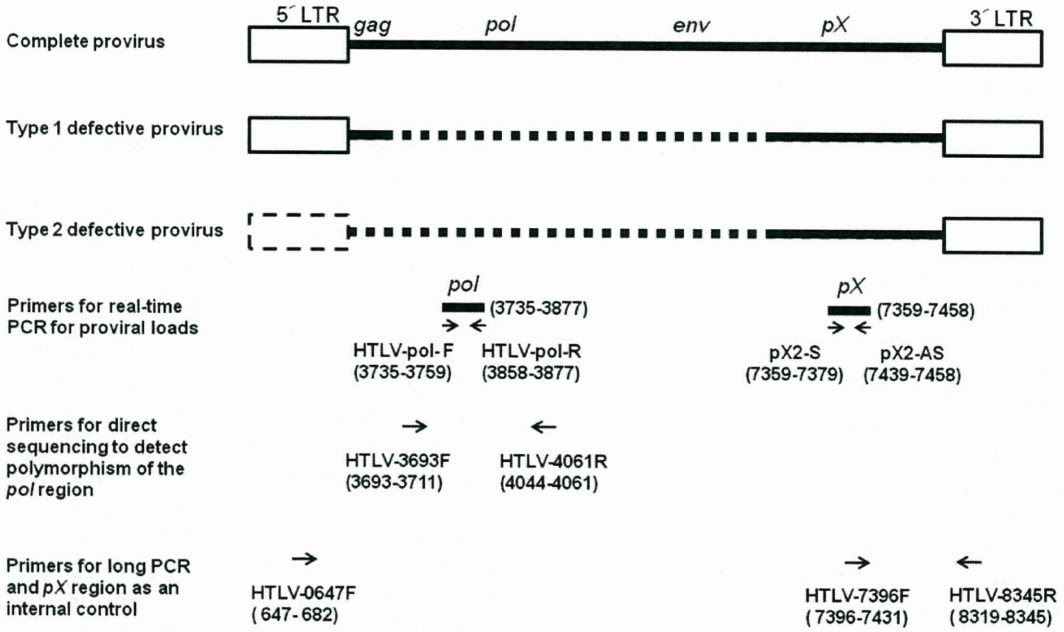

Figure 1. Schemas of structure of complete, Type 1 defective and Type 2 defective HTLV-1 (human T-lymphotropic virus Type 1) provirus. Dotted lines represent the defective regions of HTLV-1 provirus. Locations of primers for polymerase chain reactions in our study are revealed.

harboring defective provirus. Time-sequential samples of greater than 10 years obtained from asymptomatic carriers with large numbers of HTLV-1-positive cells with defective provirus were analyzed.

Material and Methods

Samples

Samples of PBMCs were obtained from 208 asymptomatic HTLV-1 carriers in the Miyazaki Cohort Study.[20] Informed consent was obtained from the study participants, and the study protocol was approved by the institutional review board at the University of Miyazaki. Genomic DNA was isolated from the PBMCs of HTLV-1 carriers by sodium dodecyl sulfate-proteinase K digestion, followed by phenol-chloroform extraction and ethanol precipitation.

Quantification of HTLV-1 provirus in PBMCs

Schemas of the structure of complete, Type 1 defective and Type 2 defective HTLV-1 provirus are shown in Figure 1.[16] The nucleotide position number of HTLV-1 provirus was according to Seiki *et al.* (accession no. J02029).[21]

Proviral DNA loads (PVLs) for the *pol* (positions 3735–3877) and *pX* (positions 7359–7458) regions were measured by real-time PCR using a Light Cycler DX 400 (Roche Diagnostics, Mannheim, Germany). When multiple time-sequential samples were available from one subject, the most recent sample was used for the first screening. The primers and the probe for the *pol* region of HTLV-1 provirus were as follows: the forward primer (HTLV-pol-F 5′-AACCAATT CATTCAAACATCTGACC-3′: positions 3735–3759), the reverse primer (HTLV-pol-R 5′-GCTTTCACAGGAGCCAA TGG-3′: positions 3877–3858) and the FAM-labeled probe (5′-FAM-TGTTCCTATCTTACTCCACCACAGTCACCGA-TA MRA-3′: positions 3767–3797).[22] The primers and the probe for the *pX* region of HTLV-1 provirus were as follows: the forward primer (pX2-S 5′-CGGATACCCAGTCTACGTGTT-3′: positions 7359–7379), the reverse primer (pX2-AS 5′-CAGTAGGG CGTGACGATGTA-3′: positions 7458–7439) and the FAM-labeled probe (5′-FAM-CTGTGTACAAGGCGACTGGTGCC-TAM RA-3′).[11] *RNase* P control Reagent (Applied Biosystems, Foster City, CA) was used for the primers and the probe for human *RNase* P DNA as internal control. PVLs were shown by the copy number of HTLV-1 provirus in 100 PBMCs.

Determination of DNA polymorphism in the pol primer region

To determine whether the lower PVLs for the *pol* region compared to that for the *pX* region in a same subject was due to the polymorphism of the DNA sequence of primers for the *pol* region, DNA sequence of PCR products of the *pol* region was identified in the cases described below. Primers used for PCR for this purpose were as follows: the forward primer (HTLV-3693F 5′-CTCTGCCAAACCATAC-3′: positions 3693–3711) and the reverse primer (HTLV-4061R 5′-ATGCAAAAGTCCGAGAAG-3′: positions 4061–4044). PCR products were supplied for direct sequencing using an