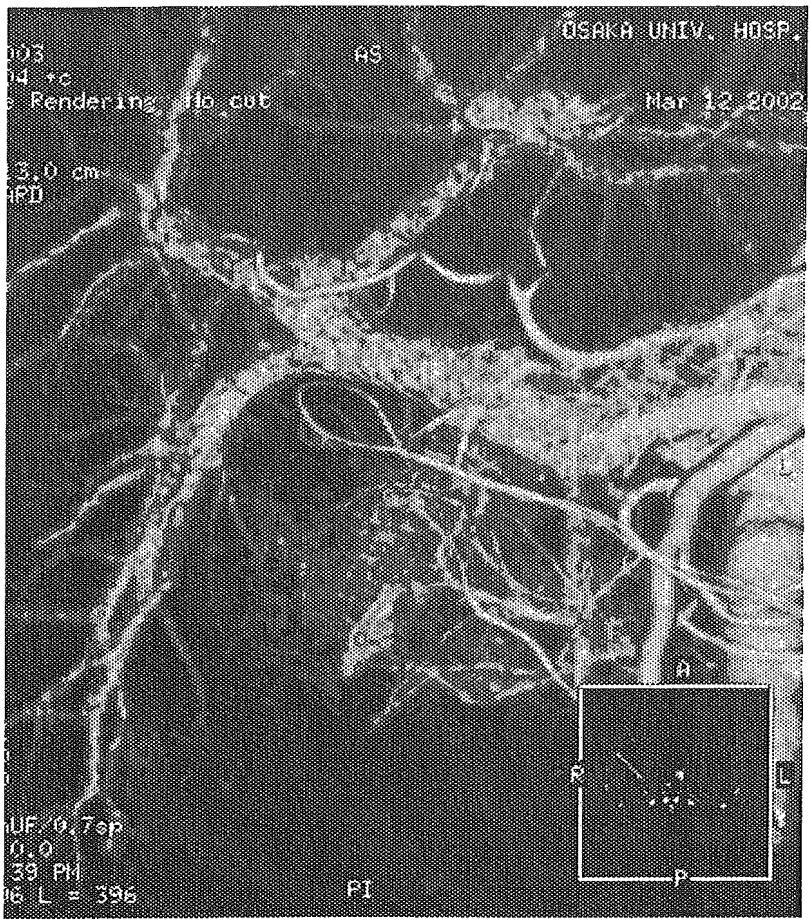

Fig. 1. Three-dimensional image from a multidetector-row CT scan. The right posterior hepatic artery passes behind the main portal vein, while the right anterior hepatic artery passes in front of the main portal vein. The right posterior portal vein branched off from the main portal vein and then divided into the right anterior portal vein and the left portal vein.

recipient's standard liver volume). The estimated volume of her left liver lobe was 385 ml (27.0% of the recipient's standard liver volume). Given the size of the recipient, a right lobe graft was thought to be necessary. The right hepatic artery was left in place because the posterior and anterior branches of the right hepatic artery were too small to reconstruct and maintain patency, even using a microscope to perform the arterial anastomosis. Thus, division and anastomosis of the donor's main portal vein after the extraction of the right lobe graft was adopted as the planned surgical strategy. A detailed explanation of the procedure and the risk to the donor was presented to the donor and other family members, and written informed consent was obtained before transplantation.

OPERATIVE TECHNIQUE

An emergent living donor liver transplantation (LDLT) was performed because of the patient's serious condition. The donor's portal vein was identified and exposed distally until the posterior and anterior branches of the right portal vein became visible, and the left portal vein was encircled distally to the trifurcation. The right hepatic artery was then exposed in the region of the portal vein. The right lobe, minus the middle hepatic vein, was then dissected. After the administration of heparin sodium (1500 units), the artery was cut at the level of the right hepatic artery (Fig. 2A) and the portal vein was transected proximal and distal to the trifurcation (Fig. 2B). The right liver lobe, weighing 602 g, was removed, and the donor's main portal vein and left portal vein were anastomosed using 6-0 Proline running sutures in an end-to-end fashion (Fig. 3).

The donor's postoperative course was uneventful. The hepatic artery and portal venous flow were examined by Doppler sonography during and after the operation; the donor's blood flow remained normal with no signs of stenosis or thrombus formation. CT examinations showed a normal-looking portal vein

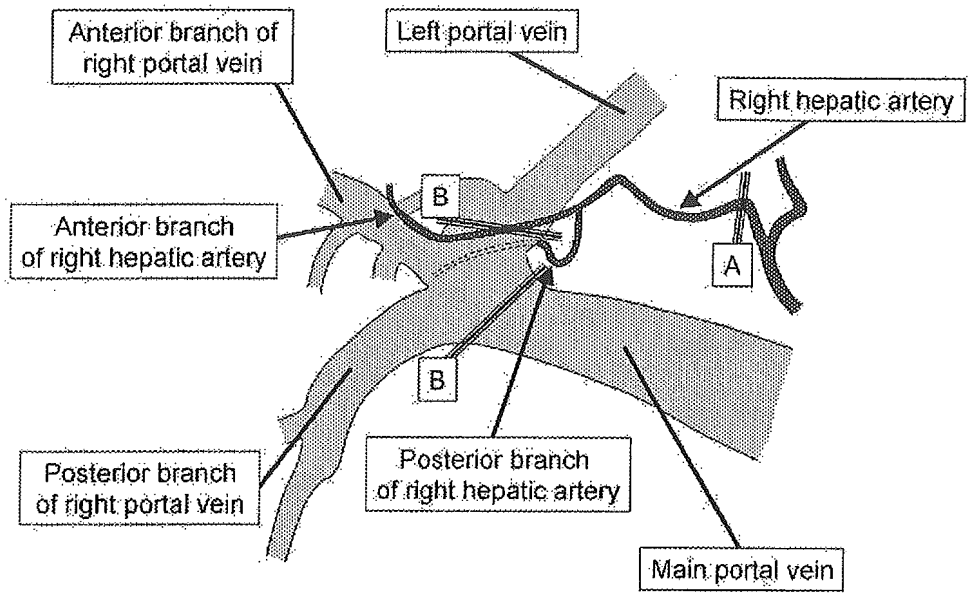

Fig. 2. Schematic view showing the three-dimensional relationship between the hepatic artery and the portal vein. The donor portal vein was transected (B), while the donor right hepatic artery was cut (A).

on postoperative days 30, 60, and 180. The donor is presently healthy and has not experienced any liver problems in the 2 years that have passed since the surgery.

The arterial and portal venous flows of the graft were also closely monitored during and after LDLT in the recipient. Although the blood flow through the hepatic vessels was excellent and showed no signs of complications, the recipient developed sepsis and died 2 months after the surgery.

DISCUSSION

Arterial and portal venous anatomies are quite important in adult-to-adult LDLTs. According to Gruttadauria et al.,[3] anomalous hepatic arteries were observed in 42% of 701 cases. The arterial anomaly presented here, in which the right anterior and posterior hepatic arteries encircled the main portal vein, belongs to type 5 of their classification system; in their series, the incidence of type 5 anomalies was 2.1%[3] and was not considered to be rare.[4] Although both arteries could have been separately anastomosed using the aid of a microscope, double arterial reconstruction in right liver lobe transplantations has been associated with an increased risk of hepatic arterial thrombosis compared with single simple reconstructions.[5,6]

Anomalies of the portal vein and its reconstruction in right lobe LDLT are also critical in many living donor cases. According to the classification of portal venous anomalies by Cheng et al.,[7] the present case belongs to the type III anomalous portal venous branching (APVB) classification. Lee et al.[8] reported that an anomalous portal venous anatomy was observed in 19 (8.9%) of 214 cases, with type III APVB anomalies accounting for 7 (3.3%) of the cases; in their series, a double anastomosis in donors with type III APVB anomalies increased the risk of portal vein thrombosis.

Portal vein reconstruction in association with a major hepatectomy is often performed for the treatment of primary hepatic cancer. Ebata et al.[9] reported that complications related to the portal vein reconstruction were not encountered in 52 consecutive cases requiring a hepatectomy with portal vein resection for the treatment of hilar cholangiocarcinoma. At our institution, we have performed more than 100 cases of portal vein reconstruction for hepatopancreatobiliary malignancies in the past 20 years and have not encountered any postoperative portal venous complications, such as portal venous thrombosis. Thus, reconstruction of the portal vein appears to be a safe technique with a very low morbidity rate.

In the case presented here, we decided to transect the donor portal vein and anastomose it in an end-to-end fashion, requiring one anastomosis of the portal vein and one anastomosis of the hepatic artery in the recipient, rather than securing the donor portal vein and producing two orifices in the right portal vein and two branches in the right hepatic artery requiring anastomoses. Although some physicians may disagree with the idea of placing the donor at risk by resecting the partial portal vein, because the safety of the living donor is of fundamental importance, we believe that

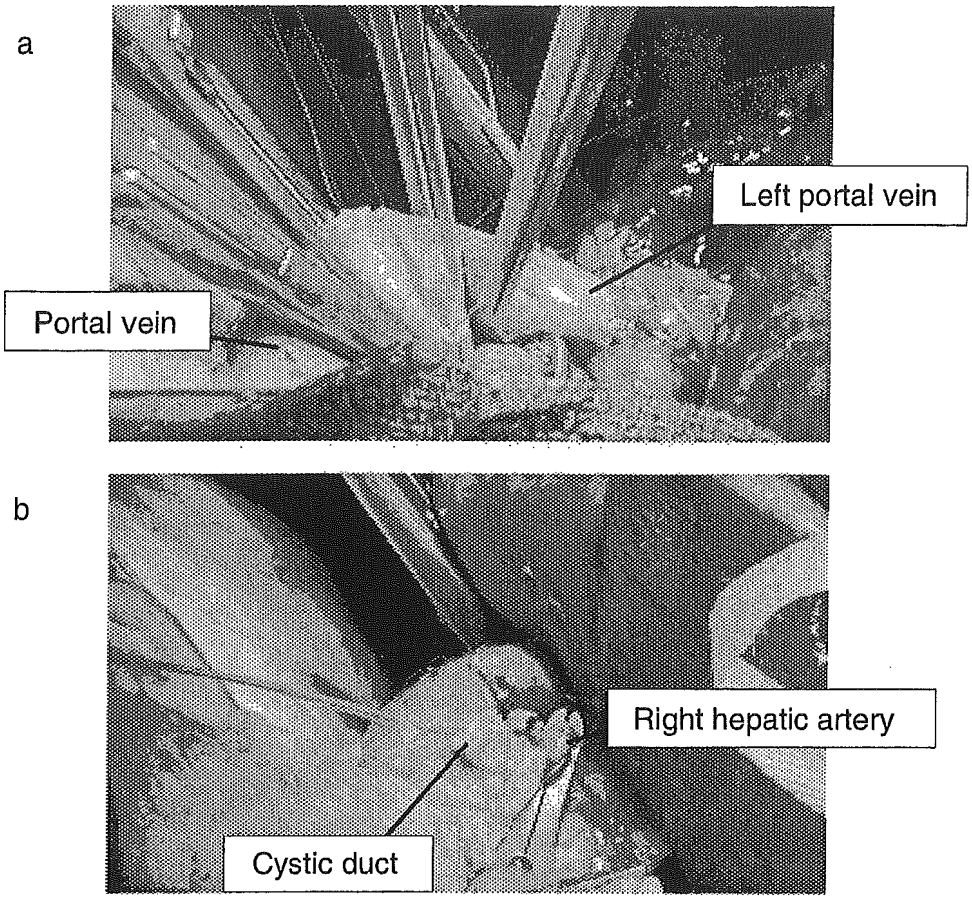

Fig. 3. (a) Reconstruction of the donor portal vein using 6-0 Proline running sutures. (b) Portal vein after declamping. Sufficient blood flow was confirmed using intraoperative Doppler sonography.

the portal venous reconstruction procedure performed in this report was justified because the risk of postoperative complications after the portal vein reconstruction was very low and the quality of the donated graft would have been poorer if double portal vein branch and double arterial branch reconstructions had been required, as discussed earlier. In this case, because the vascular anomaly was identified preoperatively, informed consent was obtained from the donor before the procedure. This case illustrates the importance of preoperative hepatic artery evaluations in addition to portal vein evaluation in all living donors to identify the feasibility of modifying vessel anastomoses in living donors, as well as recipients.

REFERENCES

1. Umeshita K, Fujiwara K, Kiyosawa K, et al. Operative morbidity of living liver donors in Japan. Lancet 2003;362:687–690.
2. Urata K, Kawasaki S, Matsunami H, et al. Calculation of child and adult standard liver volume for liver transplantation. Hepatology 1995;21:1317–1321.
3. Gruttadauria S, Foglieni CS, Doria C, Luca A, Lauro A, Marino IR. The hepatic artery in liver transplantation and surgery: Vascular anomalies in 701 cases. Clin Transplant 2001; 15:359–363.
4. Sugawara Y, Kaneko J, Akamatsu N, Makuuchi M. Arterial anatomy unsuitable for a right liver donation. Liver Transpl 2003;9:1116–1117.
5. Marcos A, Killackey M, Orloff MS, Mieles L, Bozorgzadeh A, Tan HP. Hepatic arterial reconstruction in 95 adult right lobe living donor liver transplants: Evolution of anastomotic technique. Liver Transpl 2003;9:570–574.
6. Soliman T, Bodingbauer M, Langer F, et al. The role of complex hepatic artery reconstruction in orthotopic liver transplantation. Liver Transpl 2003;9:970–975.
7. Cheng YF, Huang TL, Lee TY, Chen TY, Chen CL. Variation of the intrahepatic portal vein: Angiographic demonstration and application in living-related hepatic transplantation. Transplant Proc 1996;28:1667–1668.
8. Lee SG, Hwang S, Kim KH, et al. Approach to anatomic variations of the graft portal vein in right lobe living-donor liver transplantation. Transplantation 2003;75:S28–S32.
9. Ebata T, Nagino M, Kamiya J, Uesaka K, Nagasaka T, Nimura Y. Hepatectomy with portal vein resection for hilar cholangiocarcinoma: Audit of 52 consecutive cases. Ann Surg 2003;238:720–727.

Living-Donor Liver Transplantation with Renoportal Anastomosis for Patients with Large Spontaneous Splenorenal Shunts

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Background. End-stage liver disease is often accompanied by large spontaneous splenorenal shunts and thrombosed portal vein. Renoportal anastomosis for spontaneous splenorenal shunts in living-donor liver transplantations is one of the solutions for the treatment of these patients. However, the long-term outcome, portal venous hemodynamics after liver transplantation, and the effects of altering the renal venous drainage remained unknown.

Methods. We performed three living-donor liver transplantations with renoportal anastomosis for the treatment of spontaneous splenorenal shunts between 1999 and 2004. We then evaluated the outcome of this procedure using short- and long-term follow-ups in which the postoperative graft function, renal function, radiological images and portal hemodynamics were examined.

Results. All three patients who underwent a living-donor liver transplantation with renoportal anastomosis are alive with normal graft function and a patent renoportal anastomosis. The portal hemodynamics were similar to those in conventional living-donor liver transplantation recipients, and had no harmful effect on allograft function. Left renal function returned to normal after the temporal impairment in two cases, and remained slightly impaired in one, although it was negligible clinically.

Conclusions. Living-donor liver transplantation with renoportal anastomosis for the treatment of spontaneous splenorenal shunts in patients with end-stage liver disease is a life-saving and safe technique and should be discussed as a treatment option for patients with splenorenal shunts.

Keywords: Renoportal anastomosis, Portal vein thrombosis, Portal hemodynamics.

(*Transplantation* 2005;80: 1671–1675)

End-stage liver disease is often accompanied by portal vein stenosis or thrombosis. Although various techniques, mainly low dissections, thrombectomy of the recipient portal vein, or interposition of venous graft between the donor portal vein and the recipient SMV, have made it feasible to perform liver transplantations in patients with portal vein thrombosis, these procedures are associated with a possibility of rethrombosis and a high mortality rate (*1–4*). Patients with a complete occlusion of the portal vein and large splenorenal collaterals, a special type of portal vein thrombosis, are not uncommon, but it is sometimes technically difficult to restore portal vein flow to the graft using conventional portal vein reconstruction techniques, a portal vein thrombectomy, or the ligation of collaterals with/without a splenectomy. As a novel technique to solve the underlying problem, we previously reported the successful use of a living-donor liver transplantation (LDLT) in combination with a renoportal anastomosis procedure (RP-LDLT) for the treatment of a patient with a phlebosclerotic portal vein and large splenorenal collaterals (*5*). However, the long-term outcome, portal venous hemodynamics after liver transplantation, and the effects of altering the left renal venous drainage remained unknown in this patient. We subsequently performed two more RP-LDLT procedures. In the present study, we evaluated the efficacy of this technique for the treatment of patients with large splenorenal collaterals based on the long-term outcomes of these three patients.

PATIENTS AND METHODS

We performed 48 adult-to-adult LDLTs between March 1999 and December 2004 at our hospital. Among these patients, three adult patients had portal venous thrombosis with large splenorenal collaterals (Fig. 1A–C). Because our first attempt at performing a RP-LDLT appeared to be successful (*5*), we subsequently performed two additional RP-LDLTs using right lobe grafts. In the present study, we used prospectively collected data and evaluated the preoperative laboratory data, postoperative graft function, renal function, and short- and long-term outcomes of these three patients. We also compared portal venous flow and pressure and liver regeneration in the three RP-LDLT recipients with those of other conventional right-lobe LDLT recipients (n=23). Portal venous pressure during and after the operation were monitored in each case using a catheter inserted from a tributary of the gastroepiploic vein during the operation. Portal venous flow was also measured in each case during and after the operation using Doppler ultrasonography (SSD-6500, Aloka, Tokyo). An MD-CT scan was performed at 3, 6, and 12 months and annually thereafter; the 3D images of the vessels

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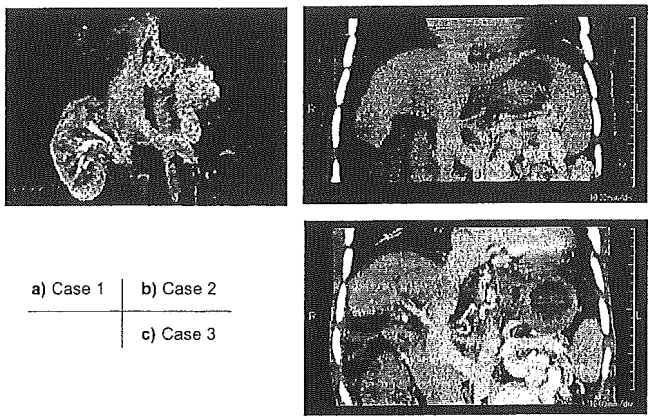

FIGURE 1. Reconstructed image of spontaneous splenorenal shunt. (A–C) Markedly dilated splenorenal shunts, pouring into the left renal shunt, are visible in all three cases. Other collaterals were small comparing with the splenorenal shunts. Left renal vein is indicated by the arrow.

were reconstructed and evaluated. A renogram using 99mTc-MAG3 was obtained to evaluate the effect of the renoportal anastomosis on renal function after the RP-LDLT procedure.

Operative Technique

The operative procedure was described previously (5). Briefly, the hepatic hilum was dissected, and the portal vein was identified. An approximately 10-cm length of the left internal jugular vein was harvested for use as an interposition vein graft (Fig. 2A). The duodenum was mobilized using the Kocher maneuver. The left renal vein was then exposed and encircled with a vessel loop. The superior mesenteric venous (SMV) pressure was measured using a catheter placed in a tributary of the SMV. An extra-corporeal veno-venous bypass was not necessary. This procedure was used in the first case but was not used in the following cases because the SMV pressure did not increase during the procedure except a short period of time from the clamping of the left renal vein to the re-perfusion to the allograft. The native liver was removed using the piggyback technique. The left renal vein was cut on the IVC. After oversewing the stump of the renal vein, the internal jugular vein was anastomosed to the left renal vein using running sutures to prepare for the portal venous anastomosis.

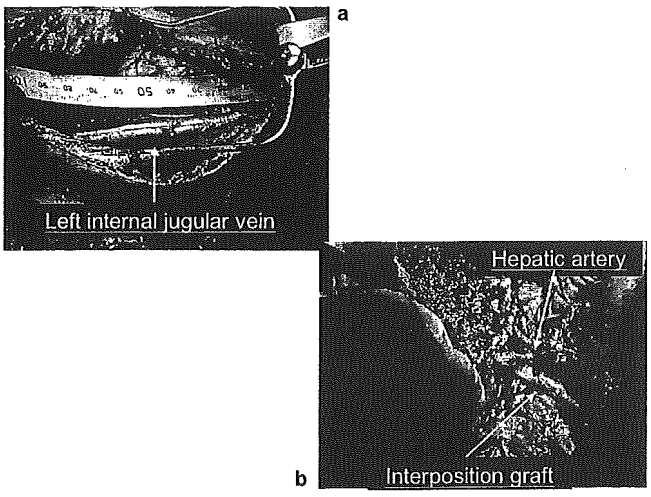

FIGURE 2. Left internal jugular vein and the reconstruction of renoportal anastomosis. (A) Left internal jugular vein of the recipient. The graft can be more than 10 cm in length. (B) Reconstructed view of the hepatic artery and portal vein anastomosed with an interposition graft during a LDLT. Sufficient blood flow was detected by an intraoperative Doppler sonography.

The right lobe of the donor was transferred to the recipient. The right hepatic vein of the graft was anastomosed to the newly created longitudinal cut on the IVC, and the right portal vein was anastomosed to the interposition vein graft using an appropriate length. After the reperfusion of the liver and the reconstruction of the anterior venous branches, the hepatic artery and biliary reconstructions were performed (Fig. 2B).

RESULTS

Among the 48 adult recipients (28 males and 20 females), three patients (6.3%) (two males and one female) had as huge spontaneous splenorenal shunts as inferior vena cava prior to undergoing an LDLT (Table 2) The mean patient age was 46.6 years (range, 19–63 years). The causes of liver cirrhosis were Primary Sclerosing Cholangitis (PSC), Laënnec cirrhosis, and Wilson disease. The second patient also had six hepatocellular carcinomas, with a maximum tumor size of 45 mm; these findings exceeded the Milan criteria (6).

Esophageal varices were present in two cases, and one case required several endoscopic ligation procedures. All three patients received ABO-identical right-lobe liver grafts from living donors. The preoperative MELD scores of the patients were 31, 14, and 29.

The portal veins were phlebosclerotic, partially or completely thrombosed, and no signals or hepato-fugal blood flow were obtained during a preoperative sonogram (Table 1).

The operative time ranged from 15 hr 55 min to 19 hr 24 min. The median operative time for conventional right lobe LDLTs at our hospital is 13 hr 18 min (10 hr 5 min 23 hr 25 min). No significant difference in the durations of the RP-LDLT and conventional right lobe LDLT procedures was observed (P=0.155). The estimated blood loss ranged from 2,000 ml to 41,000 ml. The median blood loss for right lobe LDLTs at our hospital was 6,660 ml (1,525~24,050 ml). No significant difference in the blood losses associated with the RP-LDLT and conventional right lobe LDLT procedures was observed (P=0.176). The graft weight ranged from 476 g to 766 g, and the ratio of the graft and standard liver volume ranged from 38.3% to 55.6%. The cold ischemia time ranged from 46 min to 84 min, and the warm ischemia time ranged from 41 min to 59 min. The SMV pressure was monitored during and postoperatively in the last two cases. The SMV pressure, which is representative of the pressure in the portal system, did not differ from that of conventional right-lobe LDLT recipients (Fig. 3A). The portal venous flow volume after the RP-LDLT was also similar to that of conventional LDLT recipients (Fig. 3B).

Postoperative courses of these RP-LDLT recipients

TABLE 1. Demographic and clinical characteristics

Patient no.	Age/ sex	Diagnosis	MELD	Portal vein flow	Operative time	Estimated blood loss	Type of graft	Graft liver weight	Graft liver weight: standard liver volume ratio	Interposition vein graft
1	29/F	PSC	31	Phlebosclerotic very small	15 h 55 m	2000 ml	Right lobe	766 g	56%	Left internal jugular vein
2	61/M	Laennecs/HCC	24	PVT (complete)	16 h 40 m	9300 ml	Right lobe	668 g	49%	Left internal jugular vein
3	61/M	Wilson	29	PVT (partial) Hepatofugal flow	19 h 24 m	41000 ml	Right lobe	476 g	38%	Left internal jugular vein

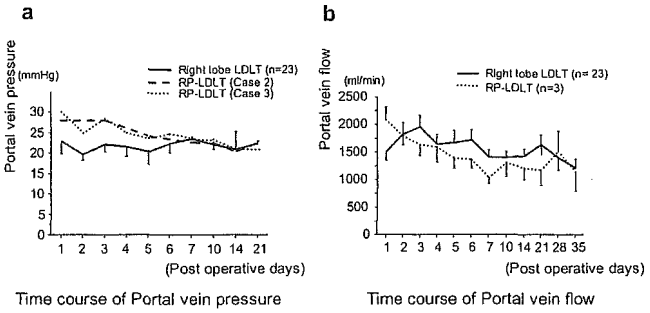

FIGURE 3. Time course of portal vein pressure and portal vein flow. (A) The portal venous pressure in the RP-LDLT recipient was slightly higher than in conventional right-lobe LDLT recipients until postoperative day 6, although the difference was not significant. (Line, right lobe LDLT (n=23), dotted line, RP-LDLT (n=3)). (B) Portal venous flow was measured using Doppler sonography and ranged from 1500 to 2000 ml/min on Day 1 and gradually decreased thereafter. The results of the two groups were similar.

were uneventful and satisfactory except pneumonia was developed and treated in Case 3 (Table 2). Liver function in the RP-LDLT recipients returned to normal, as determined by a mean total bilirubin value of less than 2.0 mg/dl on postoperative day (POD) 36, 13, and 74, respectively, whereas the average period for the other LDLT recipients was 34.7 POD (n=23, not significant). A small amount of ascites was present one month after the RP-LDLT in Cases 1 and 3. At three months after the RP-LDLT, however, CT scans showed the disappearance of the ascites in both cases. The need for diuretics was minimal, and diuretics were discontinued in all three cases within four weeks of the RP-LDLT. An MD-CT scan showed a patent renoportal anastomosis in all three cases at the time of the last follow-up (Fig. 4), which was also confirmed by the presence of hepato-petal flow on a Doppler sonography examination. The serum creatinine level was within the normal range at the 3-, 6-month, and annual follow up examinations in each case. Serial renograms after the RP-LDLT showed initial impairment of left kidney and full recovery of renal function with normal perfusion by a year after the RP-LDLT in Case 2 and 3 (Fig. 5). A slight impairment of left kidney function was shown in Case 1, although the patient was stable and the findings were clinically negligible.

DISCUSSION

Spontaneous splenorenal shunt was first described in the 18th century as a type of portosystemic shunt. Although the incidence of splenorenal shunt has not been clearly identified, several authors have described its incidence to be between 5 to 12% in cirrhotic patients (*7*). We actually encountered three cases (6.3%) of splenorenal shunt among 48 adults with end-stage liver disease.

Patients with large splenorenal shunts form a special subgroup because of their hemodynamic characteristics that SMV venous return easily leaks to large collaterals, resulting in a reduced or reversed flow in the portal vein. It is often difficult to apply a conventional liver transplantation technique to such patients with splenorenal shunt as Cescon et al. described (*8*), because the portal venous flow is essential to the transplanted livers (*9, 10*).

Large splenorenal shunts are often accompanied by portal vein thrombosis. Since the successful bypass of thrombotic segments using vein grafts (*11*) many authors have reported that liver transplantations are feasible even in the presence of portal vein thrombosis (*1–4, 12*). Nevertheless, the incidence of re-thrombosis in the portal vein after liver transplantation has been reported to be as high as 6.6 % (30 cases of re-thrombosis out of 452 cases with portal vein thrombosis) with high mortality rate by a meta-analysis (*4*). Several authors have described the incidence of re-thrombosis depends on its severity (*1–4*). Manzanet et al. (*2*) reported that the incidence of re-thrombosis in patients with partial portal vein thrombosis was 2 %, whereas that in the patients with complete portal vein thrombosis was 14.7%. The incidence of re-thrombosis in patients with portal vein thrombosis and a large splenorenal shunt under the traditional technique may be much higher than previously reported incidences for patients with portal vein thrombosis due to its hemodynamic characteristics, although no report to date has focused on this relatively less familiar kind of portosystemic shunt.

To solve these underlying problems, renoportal anastomosis for patients with a surgical splenorenal shunt in deceased-donor liver transplantations was first described by Kato et al. in 2000 (*13*). We applied this technique to a LDLT recipient, as previously reported (*5*).

TABLE 2. Outcome of the renoportal anastomosis procedure

Patient no.	Complication	Length of hospital stay	Status	Liver function	Renal function	Ascites at 3 months after transplantation	Duration of diuretics requirement	Renoportal anastomosis	Follow-up period
1	None	64 days	Alive	Good	Good	None	27 days	Patent	4 years
2	None	38 days	Alive	Good	Good	None	3 days	Patent	1 year, 8 months
3	Pneumonia (postoperative day 44)	150 days	Alive	Good	Good	None	14 days	Patent	1 year, 4 months

In our series of three RP-LDLTs, the postoperative courses of the patients were generally uneventful, and the long-term allograft and renal function were satisfactory. Although, the durations of the operations were rather long, and the blood loss in Case 3 was relatively large, these results do not mean that the RP-LDLT is a complicated and risky procedure. It is noted the operative time includes the waiting time for getting the donor graft ready and the back-table reconstruction of hepatic veins with or without interposition grafts after the hepatectomy. Sometimes, the donor liver took more than 2 hr to arrive. In fact, the duration of the RP-LDLTs was not significantly different from that of conventional LDLTs performed at our institution. As for the amount of blood loss, the preoperative condition of the third case was poor (MELD=29), the patient had a history of a prior partial hepatectomy for hepatocellular carcinoma, and a small-for-size graft was used (476 g, 38.3% of SLV). SMV pressure was around 24 to 27 mmHg during the hepatectomy and after reperfusion, which was not high enough for causing the bleeding. Furthermore, the bleeding was relatively controlled during the hepatectomy, and oozing from everywhere mainly after reperfusion of the allograft resulted in massive blood loss in this case, suggesting that the cause of the bleeding in Case 3 was coaglopathy and multifactorial, but not portal hypertension.

Renoportal anastomosis has several advantages for patients with a large splenorenal shunt. A splenectomy or ligation of the large collateral, which increases bleeding or other operative morbidity and the possibility of mortality, is not required in this technique to secure the portal venous flow to the liver. Adequate blood inflow to the portal vein of the liver graft is guaranteed, since all the blood flow in the left renal vein enters the portal vein. On the other hand, the technique also possesses some disadvantages. The large splenorenal collateral is preserved, therefore any collaterals, such as varices, will remain present and may deteriorate and bleed, causing portal hypertension after LDLT using a small graft; variceal bleeding in spontaneous splenorenal shunt patients is otherwise rare in patients who have not undergone an LDLT (*14*). Fortunately, we have not experienced any signs of postoperative growth of varices in our series. Other possible disadvantages are the injury of the liver graft from the elevated portal venous flow, renal dysfunction, anastomotic strictures or thrombosis of the interposition graft, and hypersplenism.

Renoportal anastomosis in LDLT recipients also requires an appropriate vein graft to connect the left renal vein to the portal vein of the graft liver. Since cadaveric vein grafts are rarely available in Japan, an internal jugular vein autograft, which can be 8–10 cm in length and is the same diameter as the portal vein, was removed from the recipient. The removal of the internal jugular vein does not have any harmful effects on the central nervous system (*15*). Another possible option for the vein graft would be an external iliac vein, which is usually 7–8 cm and shorter than the internal jugular vein.

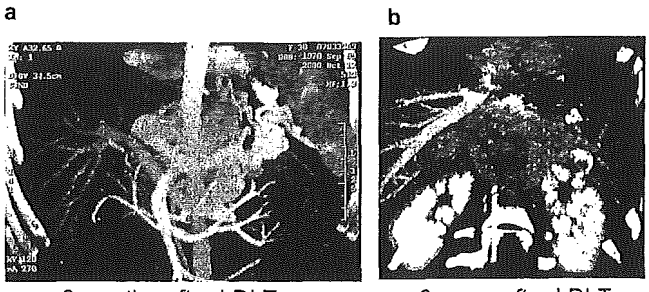

FIGURE 4. MD-CTscan after LDLT. Three months after LDLT (A) and 3 years after LDLT (B). The renoportal anastomosis is patent, and no signs of stenosis are visible in the portal system.

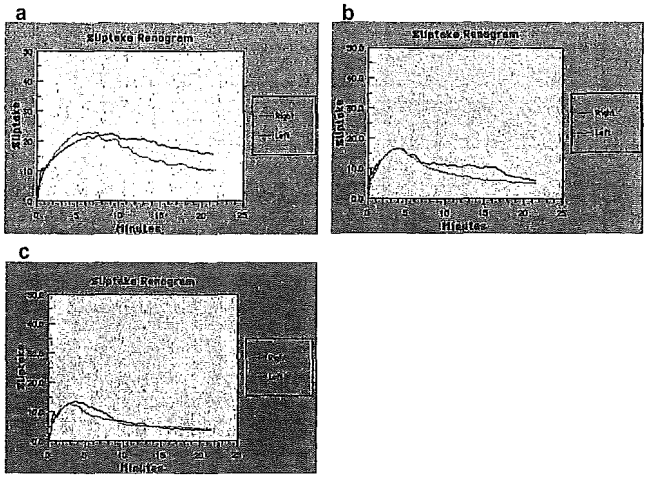

FIGURE 5. Renogram after the RP-LDLT. A renogram using 99mTc-MAG3 in Case 3 performed at 1 (A), 3 (B), and 12 (C) months after the RP-LDLT. A mild delay in accumulation and secretion in the left kidney was noted at 1 month after the RP-LDLT. Left renal function was then gradually recovered to normal by 12 months after the RP-LDLT.

The effect on portal hemodynamics was one of the major concerns in the RP-LDLT recipients. With partial liver graft LDLTs or split livers, the portal venous flow increases because of the reduced blood bed in the liver graft, resulting in the hyper-hemodynamics of the portal vein and possibly causing liver injury and impairment of the usual course of liver regeneration (known as small-for-size syndrome) (*16*). In our series, the portal venous flow was not elevated, compared to the average flow of well-functioning grafts, and the recovery of graft function did not differ from that of conventional right-lobe LDLT recipients.

The pressure of the left renal vein increases in subjects that undergo a renoportal anastomosis, possibly reducing the flow of the left renal vein. The function of the left kidney was slightly impaired in Case 1, but the findings were clinically negligible. The impairment of the left renal function may have started prior to the transplantation, since the venous pressure of the left renal vein was elevated because of the large splenorenal shunt in this particular case (*17*). In the remaining cases, left renal function was initially impaired slightly, but recovered fully by a year after the RP-LDLT, suggesting that the left renal dysfunction due to the alteration of drainage venous flow in this technique could be, if any, temporal and recovered.

Possible treatment alternatives for patients with large splenorenal shunts and insufficient portal venous flow, other than the renoportal anastomosis described here, include a portal vein thrombectomy or a thrombendovenectomy (*18*), an SMV-portal vein or collateral-portal vein anastomosis with or without an interposition vein graft, and a ligation of the splenorenal shunt with or without a splenectomy (*19*). These techniques are reportedly feasible in patients with portal vein thrombosis (*1–4*). However, the presence of large splenorenal shunts in the patients treated in these series was not noted. From the perspective of hemodynamic characteristics, simple anastomosis of the portal vein (without RP-LDLT), even if blood flow in the portal vein is present, may become inadequate and require a re-exploration to ligate the splenorenal shunt, increasing the risk of bleeding, infection, and mortality to the recipient, as described by Cescon et al. (*8*). Thus, an RP-LDLT may be the most appropriate treatment for patients with portal vein thrombus and a large splenorenal shunt, taking into account these advantages and disadvantages. Cavoportal hemitransposition is another option for these patients, but its morbidity and mortality cannot be ignored (*20*).

In conclusion, the present series of three patients suggests that hemodynamic changes in the portal venous system after the RP-LDLT were not significant and that the possible adverse effects of renoportal anastomosis, as discussed above, were clinically negligible, confirming the long-term effectiveness of the RP-LDLT. The RP-LDLT for spontaneous splenorenal shunt in end-stage liver disease patients appears to be a life-saving and safe technique and should be discussed as a treatment option for patients with splenorenal shunt.

REFERENCES

1. Yerdel MA, Gunson B, Mirza D, et al. Portal vein thrombosis in adults undergoing liver transplantation: risk factors, screening, management, and outcome. *Transplantation* 2000; 69(9): 1873.
2. Manzanet G, Sanjuan F, Orbis P, et al. Liver transplantation in patients with portal vein thrombosis. *Liver Transpl* 2001; 7(2): 125.
3. Dumortier J, Czyglik O, Poncet G, et al. Eversion thrombectomy for portal vein thrombosis during liver transplantation. *Am J Transplant* 2002; 2(10): 934.
4. Robles R, Fernandez JA, Hernandez Q, et al. Eversion thromboendovenectomy in organized portal vein thrombosis during liver transplantation. *Clin Transplant* 2004; 18(1): 79.
5. Miyamoto A, Kato T, Dono K, et al. Living-related liver transplantation with renoportal anastomosis for a patient with large spontaneous splenorenal collateral. *Transplantation* 2003; 75(9): 1596.
6. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; 334(11): 693.
7. Rousselot LM, Moreno AH, Panke WF. Studies on portal hypertension. IV. The clinical and physiopathologic significance of self-established (nonsurgical) portal systemic venous shunts. *Ann Surg* 1959; 150: 384.
8. Cescon M, Sugawara Y, Kaneko J, et al. Restoration of portal vein flow by splenorenal shunt ligation and splenectomy after living-related liver transplantation. *Hepatogastroenterology* 2001; 48(41): 1453.
9. Marubashi S, Sakon M, Nagano H, et al. Effect of portal hemodynamics on liver regeneration studied in a novel portohepatic shunt rat model. *Surgery* 2004; 136(5): 1028.
10. de Jonge J, Zondervan PE, JN, IJ, et al. Importance of portal flow diversion in experimental auxiliary partial orthotopic liver transplantation. *Transplantation* 2000; 70(1): 44.
11. Shaw Jr. BW, Iwatsuki S, Bron K, Starzl TE. Portal vein grafts in hepatic transplantation. *Surg Gynecol Obstet* 1985; 161(1): 66.
12. Stieber AC, Zetti G, Todo S, et al. The spectrum of portal vein thrombosis in liver transplantation. *Ann Surg* 1991; 213(3): 199.
13. Kato T, Levi DM, DeFaria W, et al. Liver transplantation with renoportal anastomosis after distal splenorenal shunt. *Arch Surg* 2000; 135(12): 1401.
14. Wexler MJ, MacLean LD. Massive spontaneous portal-systemic shunting without varices. *Arch Surg* 1975; 110(8): 995.
15. Rolffs J, Schmelzle R. Serious cerebral complications following unilateral ligation of the internal jugular vein. Review of the literature and a case report. *J Maxillofac Surg* 1977; 5(2): 118.
16. Man K, Fan ST, Lo CM, et al. Graft injury in relation to graft size in right lobe live donor liver transplantation: a study of hepatic sinusoidal injury in correlation with portal hemodynamics and intragraft gene expression. *Ann Surg* 2003; 237(2): 256.
17. Dash SC, Bhuyan UN, Dinda AK, et al. Increased incidence of glomerulonephritis following spleno-renal shunt surgery in non-cirrhotic portal fibrosis. *Kidney Int* 1997; 52(2): 482.
18. Molmenti EP, Roodhouse TW, Molmenti H, et al. Thrombendvenectomy for organized portal vein thrombosis at the time of liver transplantation. *Ann Surg* 2002; 235(2): 292.
19. Shapiro RS, Varma CV, Schwartz ME, Miller CM. Splenorenal shunt closure after liver transplantation: intraoperative Doppler assessment of portal hemodynamics. *Liver Transpl Surg* 1997; 3(6): 641.
20. Gerunda GE, Merenda R, Neri D, et al. Cavoportal hemitransposition: a successful way to overcome the problem of total portosplenomesenteric thrombosis in liver transplantation. *Liver Transpl* 2002; 8(1): 72.

LETTER TO THE EDITOR

Reconstruction of the middle hepatic vein in a modified right liver graft of living-donor liver transplantation while preserving the recipient's middle hepatic vein

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In living donor liver transplantation (LDLT), using a modified right liver graft, a variety of vein grafts, including from the great saphenous vein (GSV), external iliac vein (EIV) and inferior mesenteric vein (IMV), have been used for reconstruction of the middle hepatic vein (MHV) tributaries [1,2]. Each of these vein grafts has its own merits and demerits, and may or may not be suitable for venous reconstruction in a given situation [2]. We present an alternative method, in which the recipient's MHV is elongated by hepatic parenchymal transection and preserved.

The recipient was scheduled for LDLT because of acute-on-chronic hepatitis B. The donor operation, right liver harvesting, was performed in the usual manner [1]. Reconstruction of V8 was indicated by intraoperative evaluation of hepatic venous congestion [3]. In the recipient operation, after dividing the afferent vessels from the hepatic hilum, the right and left hepatic veins were severed. The MHV was preserved and clamped at its confluence with the inferior vena cava (IVC). The hepatic parenchymal transection was begun just above the MHV and the MHV was carefully dissected using a Cavitron ultrasonic surgical aspirator, with division of the MHV tributaries (Fig. 1a). The main MHV trunk was isolated and divided, and the recipient's liver was explanted, while preserving the main trunk of the MHV for a length of about 45 mm from the IVC (Fig. 1b). Then, the graft liver was placed orthotopically. The graft V8 was anastomosed end-to-end to the preserved recipient's MHV (Fig. 1c); the preserved MHV was large enough to allow anastomosis to the graft V8. Upon reconstruction of the inflow, adequate hepatic venous drainage of the reconstructed V8 was confirmed by intraoperative Doppler ultrasonography. Doppler ultrasonography on Postoperative day 30 also confirmed excellent blood flow in the reconstructed V8.

The diameter of the GSV is often small and not suitable for vein grafting for the large MHV tributaries. The EIV is large in diameter, but too short, and its harvesting is sometimes associated with congestion of the lower extremities. The IMV differs in diameter among individuals, and is, therefore, not always suitable for a vein graft. This reconstruction technique, using the preserved recipient's MHV elongated by hepatic parenchymal transection,

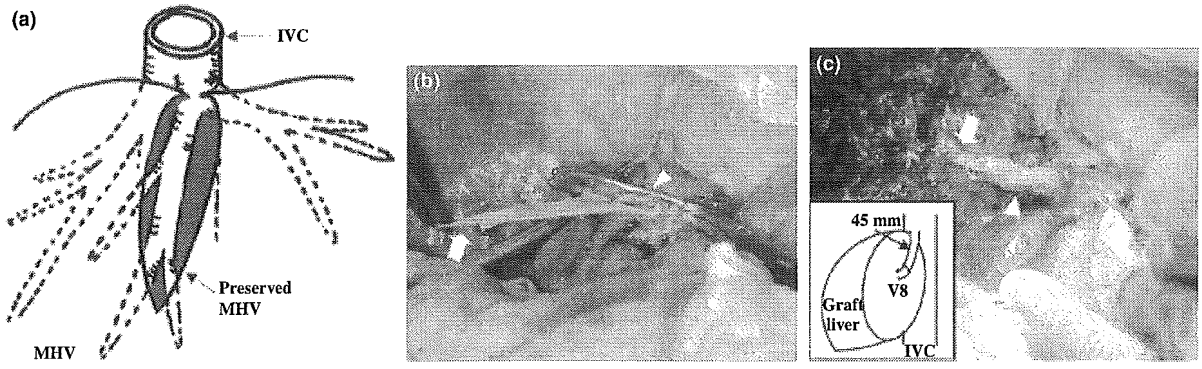

Figure 1. (a) Preservation of the recipient's middle hepatic vein (MHV) elongated by hepatic parenchymal transection; hepatic parenchymal transection was begun just above the main trunk of the MHV, and the MHV was dissected carefully and preserved. (b) Recipient after hepatectomy; the recipient's MHV was elongated by hepatic parenchymal transection, and an approximately 45-mm long segment, about 10 mm in diameter, was preserved (arrow). The left hepatic vein was divided at its confluence with the MHV (arrowhead). (c) Reconstruction of the V8 of the graft liver; the graft liver was placed orthotopically, and the recipient's elongated and preserved MHV (arrowhead) was anastomosed end-to-end to V8 (arrow).

offers several merits over those using other autogenous vein grafts. First, the native MHV-IVC anastomosis simplifies the surgical procedure by reducing the number of anastomoses to one, and the natural curvature of the MHV allows smooth drainage into the IVC. Second, the preserved MHV in the recipient is usually large enough to allow reconstruction of the MHV tributaries. Third, the need for additional surgery to harvest the vein graft is eliminated. Several demerits have also been recognized. First, this technique cannot be used in cases of malignancy for fear of dissemination of the malignant cells. Second, dissection of the recipient's MHV is a complicated procedure.

In summary, this reconstruction technique has several merits and demerits, and is worth considering as an option in cases where no other venous grafting technique is suitable.

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References

1. Sugawara Y, Makuuchi M, Sano K, *et al.* Vein reconstruction in modified right liver graft for living donor liver transplantation. *Ann Surg* 2003; **237**: 180.
2. Lee S, Park K, Hwang S, *et al.* Anterior segment congestion of a right liver lobe graft in living-donor liver transplantation and strategy to prevent congestion. *J Hepatobiliary Pancreat Surg* 2003; **10**: 16.
3. Sano K, Makuuchi M, Miki K, *et al.* Evaluation of hepatic venous congestion: proposed indication criteria for hepatic vein reconstruction. *Ann Surg* 2002; **236**: 241.

特集 生体肝移植—最新の話題

C型肝硬変に対する肝移植*

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キーワード：肝移植，C型肝炎

要旨：C型肝硬変に対する肝移植は，欧米では肝移植の40%を超える主要原因であり，わが国においても成人間生体肝移植が拡まるとともに急速に増加している．しかし，肝移植後の成績はC型肝炎の再発や肝硬変への進行が起こることから，ほかの原因に比べて劣っている．この肝移植後C型肝炎再発に対し，これまでさまざまな取り組みがなされてきたが，現在のところ，残念ながら確実に再発予防あるいは治療する方法はいまだない．本稿では，C型肝炎に対する肝移植における，肝炎再発に対するこれまでの取り組みと，当科での工夫および成績について報告する．

はじめに

C型肝炎は日本で約200万人が感染していると推測されており，今後もその数は増加すると予想されている[1]．欧米における脳死肝移植では，C型ウイルス性肝硬変が原因疾患の約4割を占め，肝移植の最も多い適応疾患となっている．

近年，わが国においても成人間生体肝移植が増加し，小児生体肝移植を凌ぐ勢いで増加しており，これに伴いC型ウイルス性肝硬変や肝細胞癌に対する生体肝移植が増加している．2004年の日本肝移植研究会[2]の統計によると，2003年12月までに行われた成人間生体肝移植は1,365例で，HCV陽性であった症例は298例であった．このようにC型肝炎は肝移植の主要原因となっているものの，C型ウイルス性肝硬変に対する脳死肝移植の成績がほかの疾患と比べて劣っていることが問題となっている．肝移植後にC型肝炎がほぼすべての患者で再発し[3,4]，移植後5年間で実に約30%の患者で肝硬変に至ることが報告されている[5]．このC型肝炎の再発が，C型ウイルス性肝硬変患者の肝移植後の長期予後を低下させる原因となっている．この肝移植後C型肝炎再発に対し，これまでさまざまな取り組みがなされてきたが，残念ながら確実に再発予防あるいは治療する方法は現在のところまだない．

本稿では，C型肝炎に対する肝移植における肝炎再発に対するこれまでの取り組みと，当科での工夫および成績について報告する．

C型ウイルス性肝硬変に対する肝移植

C型ウイルス性肝硬変に対する肝移植の成績は，これ以外の原因の肝移植と比べやや劣る．これはC型肝炎の再発が肝移植後の長期予後に影響している結果である[6,7]．肝移植後のC型肝炎再発の危険因子については様々な報告がある．急性拒絶反応やステロイドの投与，OKT3の使用はC型肝炎再発を増加すると報告されている[5,6,8]．また，ステロイドの短期投与やミコフェノール酸モフェチル（セルセプト®），カルシニューリン阻害剤が再発危険因子との報告もあるが，反対の結果も報告されており，因果関係ははっきりしていな

い．HCV のジェノタイプは 1b ではインターフェロンに効きにくく，また，肝炎再発，肝硬変になりやすく，成績が悪い[3,5,9]．最近ではドナー年齢が注目されている．高齢のドナーでは HCV 再発頻度が増すことが報告されているが，何歳以上でどれだけ危険かなどの詳細は不明である．ただし，ドナー年齢は関係ないという報告もあり，いまだ結論は出ていない．サイトメガロウイルス感染症は，C 型ウイルス性肝硬変に対する肝移植後のグラフト損失の独立危険因子であると報告されている[10]．

C 型肝炎の再発を診断するには，血液検査による肝逸脱酵素の上昇や末梢血 HCV-RNA の上昇などが参考になるが，肝生検による組織学的診断が必須である．肝炎再発の診断には，拒絶反応との鑑別や画像診断によるほかの合併症との鑑別などが重要であるが，診断困難な場合もよく経験される．肝生検は侵襲的検査であるが，正確な診断が免疫抑制剤や抗ウイルス治療には必要であること，また，早期の病理組織診断が長期予後を推察するのに有用であることから，定期的な肝生検（プロトコール肝生検）が推奨されている[11]．

C 型肝炎に対する治療は後述するとおり，インターフェロンとリバビリンが主体となって試みられているが，その成績は満足できるものではない．最近の報告では B 型肝炎の予防法に習い，human hepatitis C immune globulin（以下，HCIG）を投与する方法が試みられている．しかし，肝移植患者に安全に投与することができたが HCV-RNA 量は減少しなかったとのことで，残念ながら HCIG が有効であったとは言えず，さらなる工夫が必要である[12]．

■■■

C 型肝炎に対する予防・治療法

C 型肝炎に対する予防・治療法は大きく分けて（1）移植術前治療，（2）肝移植術後予防法（pre-emptive therapy after transplantation），（3）肝炎再発後の治療の 3 つに大別できる．

1．移植術前治療

肝移植手術時の HCV-RNA ウイルス量が多いほうがより急速に HCV 再発が起こることが報告されていることから，手術時のウイルス量を最小限にする目的で術前インターフェロンを投与することが試みられてきた．インターフェロン術前投与の効果は認められたものの，その投与には血小板減少などの副作用が伴うため，使用可能な患者は限られている．また，肝移植可能な患者がインターフェロン投与の副作用によって移植ができなくなる可能性もあり，術前使用は必ずしも推奨されない．この副作用を軽減するため，Everson ら[13]は低用量の PEG インターフェロン＋リバビリンを使用するプロトコール（low grade accelerating dosage regimen：LADR）を試み，46％の患者で移植時 HCV-RNA の陰転化することができた．ただし，治療中 4 人（3.3％）の死亡と 15 人（12％）に重篤な副作用が生じたことから，この治療法の応用には慎重にならざるを得ない．

2．肝移植術後予防法（preemptive therapy after transplantation）

術後早期にインターフェロンを使用するという報告は Singh ら[14]あるいは Scheiher ら[15]によってなされた．さらにインターフェロンとリバビリンの併用療法を術後早期から始める予防法が試みられ，治療の副作用（血小板減少，貧血，うつなど）によるドロップアウトを最小限にするため，低用量インターフェロン＋リバビリンによる予防法が行われている．効果的であるという報告と，それでもやはり副作用により治療継続が困難な症例が大半を占めたという異なる報告があり，その有効性については結論が出ていない．

3．肝炎再発後の治療

C 型肝炎に対する治療は，インターフェロン単剤からインターフェロン＋リバビリン併用療法，さらには pegylated インターフェロン＋リバビリン療法へと進化してきた．これに伴い，治療成績も徐々に改善している（**表 1**）．最新の報告では 12 か月間の治療後，SVR は 30～40％と好成績を収めている．

■■■

免疫抑制剤

免疫抑制剤を使用していない非移植患者の C 型肝炎感染の進行と比べ，肝移植後の C 型肝炎の

表1　肝移植後C型肝炎再発に対する抗ウイルス治療

著者	発表年	研究デザイン	抗ウイルス療法	患者数	IFN（MU）/RBV（mg）	期間（月）	ETR	SVR
Wright	1994	Pilot	IFN	18	3 tiw	≥4	28	0
Vargas	1995	uncontrolled (IFN vs. none)	IFN	7 vs. 7	3 tiw	6	0	0
Feray	1995	uncontrolled (IFN vs. none)	IFN	14 vs. 32	3 tiw	6	12	7
Gane	1995	Pilot	Ribavirin	7	1,200	6	0	0
Singh	1996	Pilot	IFN	18	3 tiw	6	—	—
Cattral	1996	Pilot	Ribavirin	9	800～1,200	3	0	0
Bizollon	1997	Pilot	IFN＋Ribavirin	21	3 tiw/600～1,200	6	48	24
Kizilisik	1997	uncontrolled (RBV vs. IFN /RBV vs. none)	IFN＋Ribavirin	3 vs. 3 vs. 13	600～1,200 or 3 tiw/600～1,200 or none	6	0	0
Gane	1998	RCT (IFN vs. RBV)	IFN or Ribavirin	14（IFN） vs. 14（RBV）	3 tiw vs. up to 1,200	6	0 vs. 0	0
Cattral	1999	Pilot	Ribavirin	18	600～1,200	12～44	0	0
Fisher	1999	Pilot	IFN＋Ribavirin	8	3 tiw/1,200	≥12	0	0
Cotler	2001	RCT (IFN vs. none)	IFN	8 vs. 4	3 daily	12	13	13
Gopal	2001	Pilot	IFN＋Ribavirin	12	1～3 tiw/600～1,200	Variable	50	8.3
Ahmad	2001	uncontrolled (IFN vs. IFN/RBV)	IFN＋Ribavirin	40（IFN） vs. 20 （IFN/RBV）	3 tiw vs. 3 tiw/1,200	12	15 vs. 40	2.5 vs. 20
Alberti	2001	Pilot	IFN＋Ribavirin	18	3 tiw/600	12	44	27
DeVera	2001	Pilot	IFN＋Ribavirin	32	1.5～3 tiw/600～1,000	≥12	9	9
Kornberg	2001	Pilot	IFN＋Ribavirin	15	3 tiw/600	12	64	—
Firpi	2002	Pilot	IFN＋Ribavirin	54	3 tiw/800～1,000	12	38	30
Lavezzo	2002	uncontrolled (IFN 6 m vs. IFN 12 m)	IFN＋Ribavirin	27 vs. 30	3 tiw/800	6 vs. 12	33 vs. 23	22 vs. 17
Samuel	2003	RCT（IFN/RBV vs. none）	IFN＋Ribavirin	28 vs. 24	3 tiw/1,000～1,200	12	32 vs. 0	21.4 vs. 0
Rodriguez -Luna	2004	Pilot	IFN＋Ribavirin	37	0.5～1.5 μg/kg/wk (PEGIFN)/400～1,000	12 after VR	37	26
Dumortier	2004	Pilot	PEGIFN ＋Ribavirin	20	0.5～1 μg/kg/wk (PEGIFN)/400～1,200	12	55	45
Abdelmalek	2004	Pilot	PEGIFN ＋Ribavirin	119	1.5～3 tiw or PEGIFN/400～1,000	12	24.3	24.3
Stravitz	2004	Retrospective	PEGIFN ＋Ribavirin	26	1.5～3 tiw or PEGIFN/600～1,000	12	48	35
Castells	2005	uncontrolled (PEGIFN vs. none)	PEGIFN ＋Ribavirin	24 vs. 24	1～1.5 μg/kg/wk (PEGIFN)/600～800	12	62.5	34.7

ETR：end of treatment response. SVR：sustained viral response. RCT：randomized control trial. IFN：interferon. RBV：ribavirin. tiw：週3回. PEGIFN：pegylated interferon.

進行は速い．これは免疫抑制剤によると考えられ，これまで免疫抑制剤とC型肝炎に関するさまざまな報告がなされている．免疫抑制剤は（1）ステロイド，（2）カルシニューリン阻害剤，（3）そのほか，と分けることができる．

1．ステロイド

ステロイドはHCVのreplicationを促進することが示されており，肝移植後に投与されたステロイド総量やステロイドパルスの有無とC型肝炎の再発とが関連すると報告されている．したがって，多くの施設ではC型肝炎再発を抑えるべく，早期のステロイド離脱を標準としている．しかし，逆に1年以上の長期にわたってステロイドを使用したほうがC型肝炎の進行を抑えるという報告もあり[16]，ステロイドのC型肝炎ウイルスに対する影響は明らかでない．ステロイドは当初から必須の免疫抑制剤として活躍してきたが，耐糖能異常や高血圧，感染，成長障害といった副作用が問題となり，脳死肝移植ではステロイドをまったく使用しない免疫抑制法が確立されてきた[17]．C型肝炎への影響が注目されるものの，いまのところ脳死肝移植においてステロイドフリー免疫抑制がC型肝炎再発を有意に抑制したという報告はない．一方，成人間生体肝移植でも安全にステロイドフリー免疫抑制法が施行できることが報告され[18]，C型肝炎に対する効果が期待される．ステロイド投与とC型肝炎再発との関連については現在，厚生労働科学研究費補助金「C型肝炎への肝移植後の免疫抑制法に関する研究」班で多施設共同研究を展開中である．

2．カルシニューリン阻害剤

カルシニューリン阻害剤として移植後の免疫抑制の中心となっているタクロリムス，シクロスポリンであるが，タクロリムスはFK binding proteinと，シクロスポリンはcyclophilinと結合するため，その作用はやや異なる．最近の実験では，C型肝炎ウイルスに対してシクロスポリンが抑制的に働くことが示され，両者のC型肝炎に対する働きが注目されている．しかし，肝移植後のC型肝炎の再発に関するこれまでの報告では両者の違いは認められていない．両者の差よりは，カルシニューリン阻害剤を使用すること自体がC型肝炎の進行を促進するためと考えられる．

3．そのほか

1）ミコフェノール酸モフェチル（MMF）

MMFは抗ウイルス剤であるリバビリンと構造が類似しており，抗ウイルス作用が期待されていた．MMFのC型肝炎に対する影響は色々な報告があるものの，最近のRCT（randomized controlled trial）研究の結果，抗ウイルス効果はないと結論されている[19]．

2）抗リンパ球抗体

OKT-3の使用はC型肝炎の再発を増加させるという報告と，あまり関係がないという双方の結果がある．抗IL-2受容体（CD25）抗体を使用するとC型肝炎が進行するという報告もある一方で，最近の報告では抗IL-2受容体（CD25）抗体を用いたステロイドフリー免疫抑制法がHCVに抑制的に働くようである[20]．

■■■

生体肝移植と脳死肝移植

生体肝移植が成人に応用されはじめた当初，生体肝移植では脳死肝移植に比べてC型肝炎の再発がより急速に進行するのではないかとの報告があいついだ[21,22]．これは，（1）生体肝移植では胆管合併症が高頻度に起こること，（2）血縁者からの提供の場合のHLA適合性，（3）肝再生が必要なこと，などがHCVのreplicationを増加させC型肝炎の再発を進行させる原因と予想された[23]．しかし，その後の報告では，生体肝移植でもC型肝炎の進行は脳死肝移植と比べ変わらないとするものもあり[24,25]，一定の結論は得られていない．現時点では，生体肝移植後のC型肝炎再発は脳死肝移植と同様であると考えるべきである．したがって，C型肝炎に対する予防・治療も同様の取り組みが必要と考えられる．

■■■

当施設におけるC型ウイルス性肝硬変に対する生体肝移植

これまで述べてきたように，C型肝炎は肝移植後ほぼ確実に再発して患者・グラフト生存率を低下させる原因であることから，成績向上のために

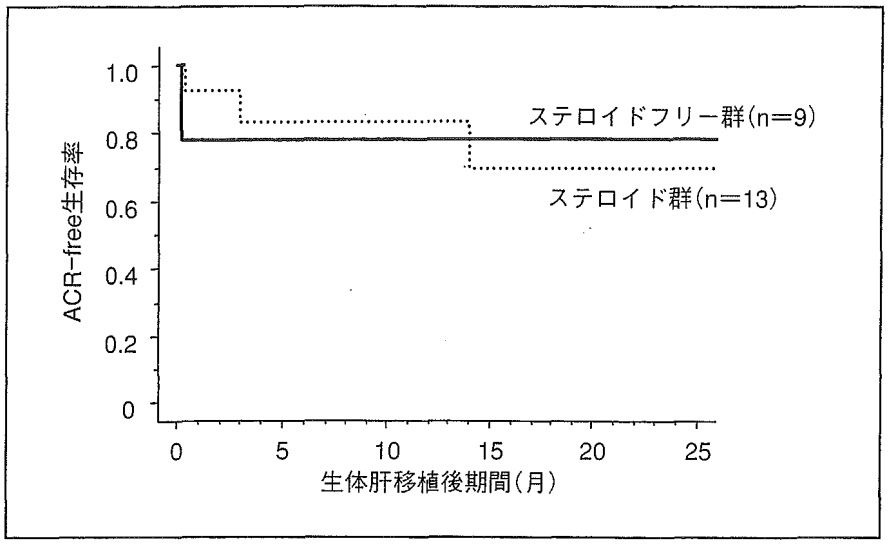

図1　ステロイドフリー免疫抑制療法における急性拒絶反応

は工夫が必要である．われわれはC型肝炎陽性レシピエントに対し，(1) ステロイドの使用を避けるステロイドフリー免疫抑制法，および (2) 術後早期に開始する予防的低用量インターフェロン＋リバビリン療法，を行ってきた．

1. ステロイドフリー

ステロイドの使用を避けることと同時に拒絶反応を起こさないようにするため，カルシニューリン阻害剤とミコフェノール酸モフェチル，抗IL-2受容体抗体を使用するステロイドフリー免疫抑制療法を行っている．ステロイドフリー免疫抑制法を用いた9例の肝移植レシピエントとステロイドを使用する従来の免疫抑制療法の12例を比べたところ，急性拒絶反応はステロイド群23.1%，ステロイドフリー群22.2%と差がなく，患者・グラフト生存率にも差を認めなかった（**図1**）．成人間生体肝移植においてステロイドフリーが安全に行うことが可能であったとともに，HCVのreplicationを抑制している可能性が示された[18]．これらの結果を，さらに大きな症例数で検証することが必要である．

2. 予防的低用量インターフェロン＋リバビリン療法

インターフェロン＋リバビリン療法はHCVに対し効果的であるが，肝移植レシピエントに使用したこれまでの報告では，その効果は満足できるものではない．その一番の問題点は，インターフェロンあるいはリバビリンによる副作用によって治療が継続できなくなることである．C型肝炎の再発は術後早期のHCV-RNA量に関係があることや，肝炎が再発してからでは治療成績が不良であることなどから，われわれは可能な限り術後早期から予防的低用量インターフェロン＋リバビリン療法を行ってきた．

インターフェロンはインターフェロン2α 150万単位×週3回，あるいはPEGインターフェロン（ペガシス®90μg/週，あるいはペグイントロン®1μg/kg/week）を投与し，また，リバビリンは400 mg/日から臨床経過をみながら増量し，また必要に応じてG-CSFの投与や休薬を行った．2004年末までに行ったHCV陽性レシピエント12名（男性7，女性5）のうち早期にグラフトを失った1名，血小板減少のため治療開始できなかった1名，HCV-RNAが自然に陰転化した1名の計3名を除く9名（平均観察期間20か月）に対し本治療を行った（**図2**）．このうち1名は投与2週で急性拒絶反応のため投与を中止した．残る8名のうち6名は肝炎再発を認めておらず，このうち2名では末梢血HCV-RNAは陰性化した．残りの2名は肝炎再発を認めたが，このうち1名は抗ウイルス治療を継続することによって肝移植後19か月目にHCV-RNAがDNAプローブ法で感度以下となり，組織学的にも改善を認めた．いまだ症例数，観察期間ともに不十分であるものの，

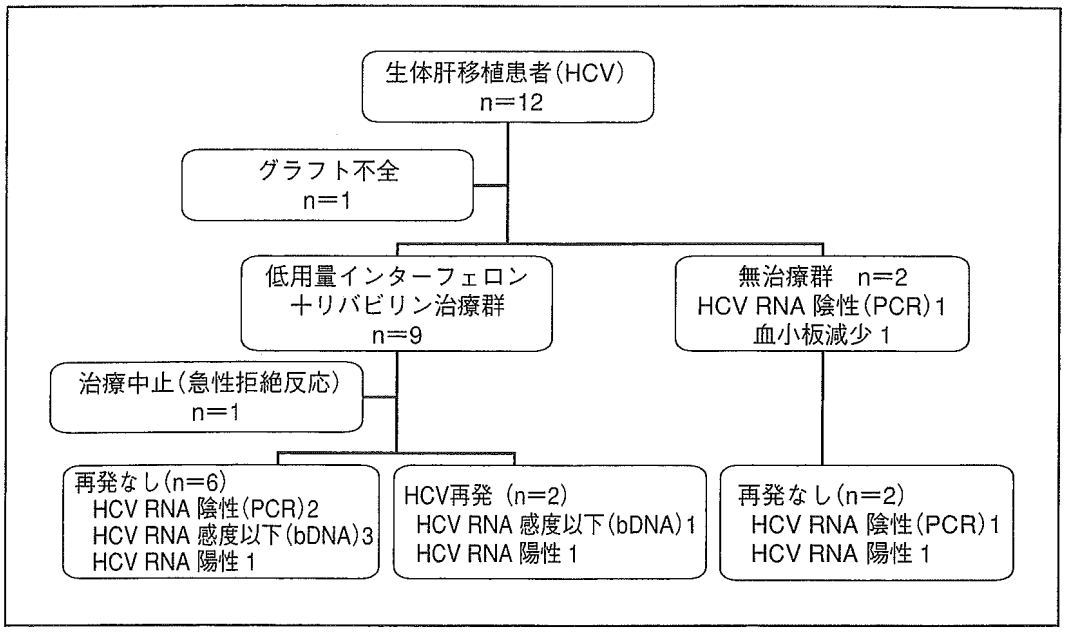

図2　当施設における抗 HCV 治療法の概要

予防的低用量インターフェロン＋リバビリン療法を患者に合わせ治療を継続するというわれわれのプロトコールはC型肝炎陽性レシピエントの予後を向上させるものとして期待している．

■■■

おわりに

近年，肝移植の適応疾患は脳死・生体肝移植のいずれにおいても大きく様変わりし，C型肝炎は原因疾患の筆頭となった．このC型肝炎に対する肝移植はいまのところ多くの解決すべき問題を抱えており，肝移植における現在の最大のトピックスの1つである．これまでに数多くの報告があるものの，残念ながら現時点で推奨される免疫抑制法や再発予防法はいまだ存在しない．

現在，利用できる範囲で最適な免疫抑制療法の探求や正確な再発予測・危険因子の解明はもちろん，新たな免疫抑制剤や抗ウイルス治療薬の開発や応用も必要であり，われわれに課せられた課題は大きい．これらの問題を解決し，C型肝炎に対する肝移植の成績が少しでも向上するように，今後のさらなる研究に大いに期待したい．

文　献

1) Yoshizawa H：Hepatocellular carcinoma associated with hepatitis C virus infection in Japan：projection to other countries in the foreseeable future. Oncology **62**：8-17 (Suppl 1), 2002
2) 日本肝移植研究会：肝移植症例登録報告．移植 **39**：634-642，2004
3) Gane EJ, Portmann BC, Naoumov NV, et al：Long-term outcome of hepatitis C infection after liver transplantation. N Engl J Med **334**：815-820, 1996
4) Berenguer M, Lopez-Labrador FX, Wright TL：Hepatitis C and liver transplantation. J Hepatol **35**：666-678, 2001
5) Prieto M, Berenguer M, Rayon JM, et al：High incidence of allograft cirrhosis in hepatitis C virus genotype 1b infection following transplantation：relationship with rejection episodes. Hepatology **29**：250-256, 1999
6) Neumann UP, Berg T, Bahra M, et al：Long-term outcome of liver transplants for chronic hepatitis C：a 10-year follow-up. Transplantation **77**：226-231, 2004
7) Berenguer M, Prieto M, Rayon JM, Mora J, et al：Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. Hepatology **32**：852-858, 2000
8) Testa G, Crippin JS, Netto GJ, et al：Liver transplantation for hepatitis C：recurrence and disease progression in 300 patients. Liver Transpl **6**：553-561, 2000
9) Gane EJ, Naoumov NV, Qian KP, et al：A longitudinal analysis of hepatitis C virus replication following liver transplantation. Gastroenterology **110**：167-177, 1996
10) Burak KW, Kremers WK, Batts KP, et al：Impact of cytomegalovirus infection, year of transplantation, and donor age on outcomes after liver transplantation for hepatitis C. Liver Transpl **8**：362-369, 2002
11) Berenguer M, Rayon JM, Prieto M, et al：Are post-transplantation protocol liver biopsies useful in the long term?. Liver Transpl **7**：790-796, 2001

肝移植後のウイルス肝炎対策
― B型肝炎 ―

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特集 ウイルス肝炎と肝移植 Ⅰ. 施設における現状と対策：全国調査より

Treatment of viral hepatitis after liver transplantation: hepatitis B

これまでにB型肝炎陽性患者に対する肝移植において，肝炎再発予防法としてHBIGとラミブジンの併用療法の安全性および有効性が示されてきた．しかし，その標準投与量や投与期間は明確には確立されていない．また，現在HBIGの保険適応はなく，患者あるいは施設がこれを負担しているのが現状である．日本肝移植研究会では，日本の各肝移植施設におけるB型肝炎の再発予防策に関するアンケートを行い，各施設での現状を調査した．この結果，各施設で投与量や時期に少々のばらつきがあるものの全体として標準的予防法が示された．

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key words : 肝移植，B型肝炎，抗ウイルス剤，免疫グロブリン(HBIG)

B型肝炎に対する有効な予防法が行われない場合，肝移植時に血清中のHBeAgあるいはHBV DNAが陽性であればB型肝炎の術後再発はまず必発で，そうでなくても50～75%に再感染することが報告されており，1980年代まで，高率に術後再発するB型肝炎に対する肝移植は禁忌とされていた．

これに対し80年代以降，周術期にB型肝炎免疫グロブリン(hepatitis B immunegloblin：HBIG)が使用されるようになり，さらにこれを術後長期(＞6カ月)にわたり投与することで，B型肝炎再発を抑制することが可能であることがわかってきた[1,2]．しかしながら，HBIG単剤の予防では3年で36%の再発があることもまた報告された[3]．

受動免疫による予防法であるHBIG投与に対し，HBVのreplicationを抑える抗ウイルス剤であるラミブジンが登場し，1990年代後半には肝移植後のB型肝炎再発予防としてさまざまな研究が行われた．ラミブジンは非代償性肝硬変患者にも比較的安全に投与でき，4週間の投与で62.5～100%の症例でHBV DNAが陰転化する．しかし，YMDD変異株が10～25%に出現することなどから，ラミブジン単剤の予防法では肝移植後のB型肝炎再発は3年で約半数にのぼることが報告された[4]．

このようにHBIGあるいはラミブジン単剤での予防には限界があることがわかった一方で，両者の併用予防法がきわめて有効であることが1998年，Markowitzらによりはじめて報告された[5]．その後の報告では，HBIGの投与スケジュールやラミブジン投与開始時期などは異なるものの，術前HBV DNAには関係なく移植術後のB型肝炎再発率はきわめて低く0～10%であると報告されている．これまでのHBIG＋ラミブジン予防法とその成績を**表1**にまとめた．

以上のように，現在ではHBIGとラミブジンの併用療法は，B型肝炎陽性患者に対する肝移植において安全かつ有効であることが示されている．しかし，その投与量や投与期間ははっきりと確立されていない．そのためこれらは各施設によって決められており，他方HBIGの保険適応は現在なく，患者あるいは施設がこれを負担しているのが現状である．また，新しい抗ウイルス剤であるアデフォビルやHBワクチンの接種といった再発予

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表1　肝移植における HBIG＋ラミブジン併用予防法とその成績

著者	発表年	患者数	肝移植術前予防と期間(月(範囲))	肝移植術後 HBV 再発予防法	HBIG の投与量	HBV 再発(%)	観察期間(月)
Markowits	1998	14	LAM 3 (0.7～7.8)	LAM + HBIG	10,000 IU × 7 日間，以後 10,000 IU/ 月	0	13
Yao	1999	10	LAM 8.6 (1～22)	LAM + HBIG	HBV DNA(+)症例：10,000 IU × 7 日間，以後 1,000 IU/3 週 HBV DNA(−)症例：術中 10,000 IU，以後 1,000 IU/ 週× 4 週間，以後 1,000 IU/ 月	10	15
McCaughan	1999	9	なし	LAM + HBIG	400 IU × 7 日間，以後 400 IU × 3 週間，以後 400 IU/ 月	0	17
Yoshida	1999	7	LAM	LAM + HBIG	2,170 IU × 15 日間，以後 2,170 IU/2 週～4 週，12 カ月まで HBs 抗体＞ 300 IU/L	0	17
Angus	2000	37	LAM 3.2	LAM + HBIG	400～800 IU × 7 日間，以後 400～800 IU/ 月	2.7	18
Marzano	2001	26	LAM 4.6 (0.6～14.1)	LAM + HBIG	術中 10,000 IU，以後 5,000 IU × 7 日間，以後 500 IU/ 週× 3 週間，以後 5,000 IU/ 月	4	30
Rosenau	2001	21	LAM 4.6 (0.06～14.1)	LAM + HBIG	10,000 IU × 4 日間，14 日まで HBs 抗体＞ 500 IU/L，15 日以後 HBs 抗体＞ 100 IU/L	9.5	21
Han	2001	59	LAM	LAM + HBIG	10,000 IU × 8 日間，以後 10,000 IU/ 月	0	15
Seehofer	2001	17	LAM 10.6 (1～28)	LAM + HBIG	10,000 IU/ 日(HBsAg(−)まで)，以後 1,500～2,000 IU/ 月，HBs 抗体＞ 100 IU/L	18	25

LAM：lamivudine

防法も各施設で工夫されている．

日本肝移植研究会(会長：門田守人)では，日本の各肝移植施設における B 型肝炎の再発予防策に関するアンケートを 2004 年度に行い，各施設での現状を調査した．このアンケート結果を報告する．

肝移植術後 B 型肝炎予防法に関する全国アンケート

肝移植研究会によると[6]，2004 年 3 月末までに行われた生体肝移植の総数は 2,667 例(18 歳以上の成人 1,365 例，小児 1,302 例)，脳死肝移植は 25 例であった．成人 1,365 例のうち HCV 陽性例は 297 例(21.8%)，HBV 陽性例は 190 例(13.9%)であった．肝移植術後成績をくらべると，HBV の成績はそれ以外の症例と同等であることがわかる(図 1)．

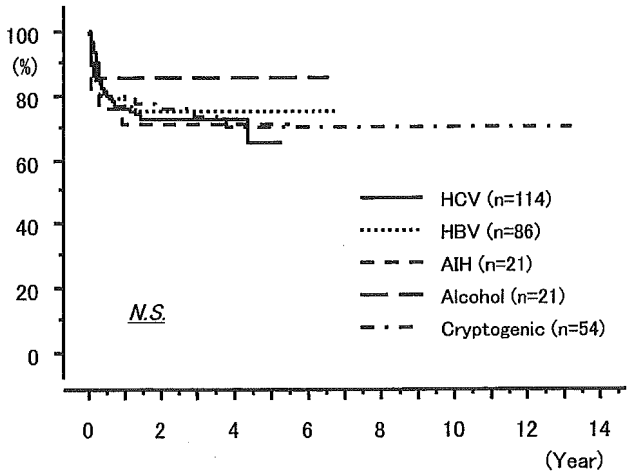

図 1　本邦における肝移植の成績
(日本肝移植研究会，2004[6]より)

肝移植研究会では，全肝移植施設にアンケートを送り，HBIG およびラミブジンの使用法について調査を行った．37 施設より回答があった．

1. ラミブジン(有効回答 26 施設)(図 2)

(1)　術前投与開始時期

肝移植術前 1 カ月前から投与を行う施設が 7 施

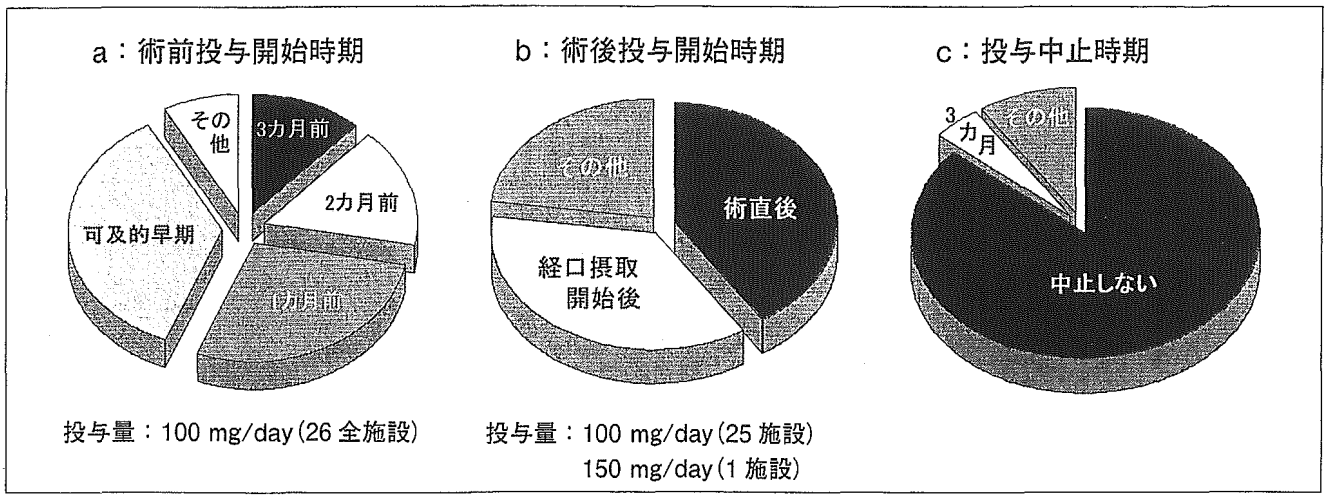

図2　ラミブジン投与に関するアンケート結果(有効回答26施設)

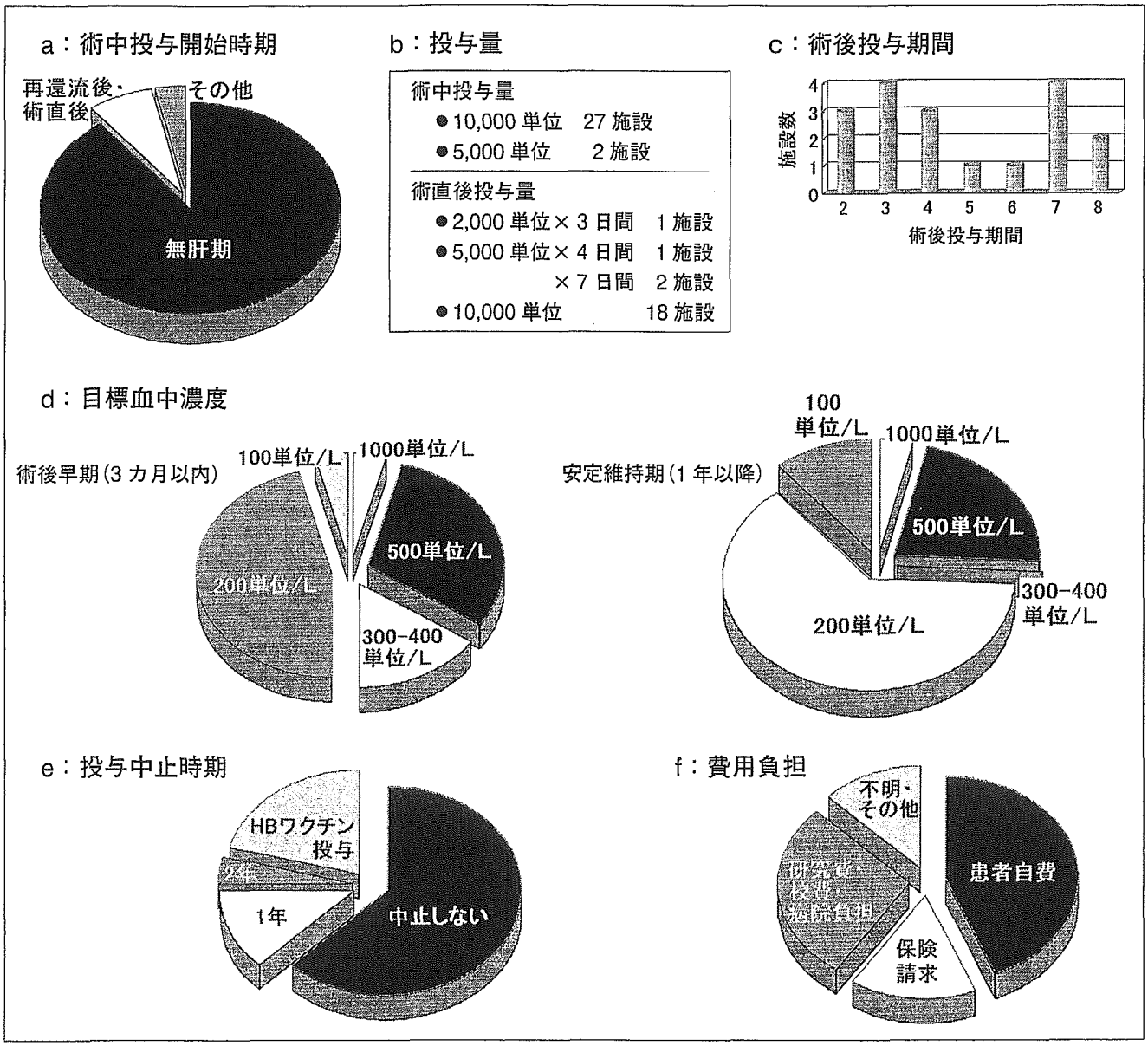

図3　HBIG投与に関するアンケート結果
(有効回答29全施設で投与)

設(28%)あり，最も多かった一方で，移植適応が決定すればすぐに投与するとした施設が9施設(36%)あった．

(2)　術前開始投与量

開始投与量はすべての施設で100 mg/日であった．ただし，腎機能に応じた投与量の変更が必要である．

(3)　術後投与開始時期

術直後からという施設が9施設(41%)，経口摂取開始後が8施設(36%)であった．

(4)　術後開始投与量

100 mg/日という施設がほとんであった．

(5)　投与中止時期

投与は中止しない施設が19施設(86%)であった．

2. HBIG(有効回答29施設)(図3)

全施設において，術中および術後に投与されている．

(1)　術中投与開始時期

無肝期に投与する施設が大多数であった．

(2)　術中投与量

1万単位の投与がほとんどの施設で行われていた．

(3)　術直後投与量

各施設によりやや異なっていた．毎日1万単位を投与する施設が18施設と最も多く，投与開始は術後3日前後あるいは7日前後が多数であった．

(4)　目標血中濃度

術後早期(3カ月以内)はHBs抗体価500単位/L以上を維持する施設が9施設(36%)，200単位/Lを維持する施設が12施設(46%)であった．安定維持期(1年以降)は500単位/L以上を維持する施設が6施設(23%)，200単位/Lを維持する施設が17施設(65%)であった

(5)　投与中止時期

15施設(63%)で中止せず投与をつづけている．5施設ではHBワクチンの接種を試みている．

(6)　費用負担

患者が負担している施設が14施設(44%)，研究費・校費等を使用している施設が9施設(28%)であった．

表2　HBIG保険適応に向けての厚生労働省への要望

HBs抗原陽性の肝移植レシピエントにおける肝移植後のHBV再感染予防

- 無肝期：10,000単位(200単位/kg)を静注．
- 術後1週間：10,000単位(200単位/kg)を連日静注．
- 術後1週間以降1年まで：HBs抗体価を1,000単位/L以上に維持するよう適宜追加静注する．
- 術後1年以降：HBs抗体価を200単位/L以上に維持するよう適宜追加静注する．

肝移植レシピエントにおける，HBc抗体陽性ドナーからの肝移植後のHBV感染予防

- 無肝期：10,000単位(200単位/kg)を静注．
- 術後4日間：10,000単位(200単位/kg)を連日静注．
- 術後5日以降：HBs抗体価を200単位/L以上に維持するよう適宜追加静注する．

(2004年9月．日本肝移植研究会)

全国アンケートのまとめ

全国調査からは以下のような結果が得られた．

1. ラミブジン

- 術前1～3カ月以上前より投与開始
- 術後も継続

2. HBIG

- 無肝期：1万単位
- 術後早期(3カ月以内)：
  HBs抗体価200～500 IU/Lを維持
- 安定維持期(1年以降)：
  HBs抗体価200(～500)IU/Lを維持
- HBワクチンを一部施設で施行
- 約半数の施設で費用は患者負担

おわりに

今回行われた肝移植患者におけるB型肝炎再発予防法のアンケートは，全国規模ではじめて行われたものである．HBIGおよびラミブジンによる併用予防法が肝移植後の標準治療として行