

Fig. 4. Case 18. Representative findings in a liver with recurrent hepatitis C. Many liver infiltrating lymphocytes were positive for CD4 and FOXP3. HAI, hepatitis activity index; RAI, rejection activity index.

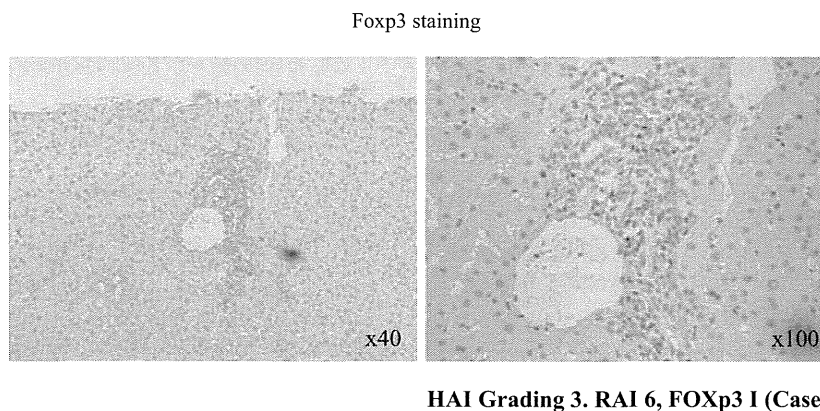


Fig. 5. Case 7. Representative findings in a liver with acute cellular rejection. Few liver infiltrating lymphocytes were positive for both CD4 and FOXP3. HAI, hepatitis activity index; RAI, rejection activity index.

addition to possible vascular abnormalities. Previously, Jain et al. (21) reported the significance of CD4 expression in infiltrating lymphocytes, as CD4, CD8, and CD56 were similar in both ACR and recurrent HCV infection. However, accurately differentiating ACR from hepatitis C can sometimes be very difficult.

In previous reports regarding LT, the significance of Tregs in the grafted liver has been controversial. One report showed a relationship between ACR and an increase in Tregs. Intrahepatic detection of FOXP3 gene expression after LT can be accomplished using minimally invasive aspiration biopsy (15). With regard to recurrent hepatitis C, FOXP3

mRNA expression was used to differentiate between the two conditions. Based on needle biopsy, they reported that intrahepatic FOXP3 levels are associated with HCV re-infection and a history of acute rejection, and that the level increased within the first year after LT (15).

Generally speaking, Tregs are associated with graft tolerance in organ transplantation. It seems likely that FOXP3 mRNA expression is associated with graft acceptance (22). It was reported that CD4+ FOXP3 cells are present within grafts in a subset of tolerant patients after human LT (23). However, in the present study, no clear relationship was observed between

ACR and Tregs, except to find a statistical difference between 0 and I in FOXP3 staining. This relationship needs further investigation without the interference of HCV infection.

Sakamoto et al. (24) reported increased expression of FOXP3 mRNA immediately after LDLT, probably because of the activation of T cells, including Tregs and other T-cell subsets. In addition, it was reported that expression of FOXP3 mRNA on days 14, 21, and 28 after transplantation were lower in recipients with ACR within 60 days after LDLT. In our study, the median time since transplantation was 270 days. This is different from previous reports, which focused on short-term diagnosis using FOXP3 staining in the liver and peripheral blood. Usually, 6 months after LT, the level of immunosuppression is stabilized. HCV infection could occur during this period, and antiviral therapy is often initiated. In our study, most patients were undergoing or had already received antiviral therapy with IFN and ribavirin. Although we showed a relationship with FOXP3 expression, we were unable to clarify the function of Tregs in recurrent HCV infection after LT. Further investigation will be needed.

After effective IFN therapy, the number of infiltrating lymphocytes seemed to decrease, which made scoring FOXP3 staining difficult. It was unclear whether the character of the infiltrating lymphocytes changed over the course of treatment. In settings other than transplantation, the FOXP3 staining system may be used to differentiate hepatitis C from autoimmune-like disease or other causes of hepatitis.

In conclusion, FOXP3 staining in infiltrating lymphocytes in the liver may represent a surrogate marker for recurrent HCV infection after LDLT.

Acknowledgements:

Authors' contributions: S.E., T.K., and K.N. carried out study conception and design. M.H. and A.S. provided acquisition of data. M.T., T.I., and H.M. performed analysis and interpretation of data. M.T. and S.E. were responsible for drafting of the manuscript. T.K., S.E., and K.N. performed critical revision.

References

1. Eguchi S, Takatsuki M, Soyama Y, et al. Intentional conversion from tacrolimus to cyclosporine for HCV-positive patients on preemptive interferon therapy after living donor liver transplantation. *Ann Transplant* 2007; 12 (4): 11–15.
2. Regev A, Molina E, Moura R, et al. Reliability of histopathologic assessment for the differentiation of recurrent hepatitis C from acute rejection after liver transplantation. *Liver Transpl* 2004; 10 (10): 1233–1239.
3. Sakaguchi S. Naturally arising CD4+ regulatory T cells for immunologic self-tolerance and negative control of immune responses. *Annu Rev Immunol* 2004; 22: 531–562.
4. Piccirillo CA, Thornton AM. Cornerstone of peripheral tolerance: naturally occurring CD4+ CD25+ regulatory T cells. *Trends Immunol* 2004; 25 (7): 374–380.
5. Jiang H, Chess L. An integrated view of suppressor T cell subsets in immunoregulation. *J Clin Invest* 2004; 114 (9): 1198–1200.
6. Sakaguchi S, Sakaguchi N, Shimizu J, et al. Immunologic tolerance maintained by CD25+ CD4+ regulatory T cells: their common role in controlling autoimmunity, tumor immunity, and transplantation tolerance. *Immunol Rev* 2001; 182: 18–32.
7. Maloy KJ, Powrie F. Regulatory T cells in the control of immune pathology. *Nat Immunol* 2001; 2 (9): 816–822.
8. Hori S, Sakaguchi S. Foxp3: a critical regulator of the development and function of regulatory T cells. *Microbes Infect* 2004; 6 (8): 745–751.
9. Coutinho A, Hori S, Carvalho T, Caramalho I, Demengeot J. Regulatory T cells: the physiology of autoreactivity in dominant tolerance and 'quality control' of immune responses. *Immunol Rev* 2001; 182: 89–98.
10. Lan RY, Ansari AA, Lian ZX, Gershwin ME. Regulatory T cells: development, function and role in autoimmunity. *Autoimmun Rev* 2005; 4 (6): 351–363.
11. Furuno K, Yuge T, Kusahara K, et al. CD25+ CD4+ regulatory T cells in patients with Kawasaki disease. *J Pediatr* 2004; 145 (3): 385–390.
12. Kukreja A, Cost G, Marker J, et al. Multiple immunoregulatory defects in type-1 diabetes. *J Clin Invest* 2002; 109 (1): 131–140.
13. Sakaguchi S. Naturally arising Foxp3-expressing CD25+ CD4+ regulatory T cells in immunological tolerance to self and non-self. *Nat Immunol* 2005; 6 (4): 345–352.
14. Miyaaki H, Zhou H, Ichikawa T, et al. Study of liver-targeted regulatory T cells in hepatitis B and C virus in chronically infected patients. *Liver Int* 2009; 29 (5): 702–707.
15. Demirkiran A, Baan CC, Kok A, Metselaar HJ, Tilanus HW, van der Laan LJ. Intrahepatic detection of FOXP3 gene expression after liver transplantation using minimally invasive aspiration biopsy. *Transplantation* 2007; 83 (6): 819–823.
16. Brown K, Wong W. Diagnostic value of regulatory T cells: a new facet of a much studied cell population. *Transplantation* 2008; 86 (11): 1485–1491.
17. Perrella A, Arenga G, Pisaniello D, et al. Elevated CD4+/CD25+ T-cell frequency and function during hepatitis C virus recurrence after liver transplantation. *Transplant Proc* 2009; 41 (5): 1761–1766.
18. Knodell RG, Ishak KG, Black WC, et al. Formulation and application of numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981; 1 (5): 431–435.
19. [Anonymous.] Banff schema for grading liver allograft rejection: an international consensus document. *Hepatology* 1997; 25 (3): 658–663.
20. Demetris A, Adams D, Bellamy C, et al. Update of the International Banff Schema for Liver Allograft Rejection: working recommendations for histopathological staging and

- reporting of chronic rejection. An International Panel. *Hepatology* 2000; 31 (3): 792–799.
21. Jain A, Ryan C, Mohanra R, et al. Characterization of CD4, CD8, CD56 positive lymphocytes and C4d deposits to distinguish acute cellular rejection from recurrent hepatitis C in post-liver transplant. *Clin Transplant* 2006; 20 (5): 624–633.
 22. Fehervari Z, Sakaguchi S. CD4+ tregs and immune control. *J Clin Invest* 2004; 114 (9): 1209–1217.
 23. Gondek DC, Lu LF, Quezada SA, Sakaguchi S, Noelle RJ. Cutting edge: contact-mediated suppression by CD4+ CD25+ regulatory cells involves a granzyme B-dependent, perforin-independent mechanism. *J Immunol* 2005; 174 (4): 1783–1786.
 24. Sakamoto R, Asonuma K, Zeledon Ramirez ME, Yoshimoto K, Nishimori A, Inomata Y. Forkhead box P3 (FOXP3) mRNA expression immediately after living-donor liver transplant. *Exp Clin Transplant* 2009; 7 (1): 8–12.

Use of stepwise versus straightforward clamping of biliary drainage tubes after living-donor liver transplantation: a prospective, randomized trial

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Abstract

Background/purpose There has been no report describing the optimal clamping method for biliary drainage tubes in living-donor liver transplantation (LDLT), although biliary splinting and drainage plays an important role in this procedure.

Methods When performing LDLT, we generally use a 2-mm drainage tube for the splint at the biliary anastomosis, and externalize it through the lower common bile duct. In the present study, when the serum levels of total bilirubin were lower than 5 mg/dl, and negativity for biliary complications and good passage of contrast media to the duodenum were confirmed, the drainage tubes were clamped. To determine the optimal clamping method, patients were randomly divided into two groups; those whose drainage tubes were subjected to stepwise clamping for 3, 6, 12, and 24 h per day ($n = 20$), and those whose drainage tubes were subjected to straightforward clamping ($n = 20$).

Results The results of liver function tests and rates of clamping failure were not different between the two groups after the different clamping methods were used.

Conclusions Straightforward clamping could be a simple and reasonable method to close a biliary drainage tube after LDLT.

Keywords Clamp · Liver transplantation · Biliary drainage · Tube

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Introduction

Biliary drainage and splinting plays an important role in living-donor liver transplantation (LDLT) because the rate of biliary complications is higher in LDLT than in deceased-donor whole LT [1, 2]. We generally use an external biliary splint and have previously reported the two-step method used for removal of the splint [3].

Anecdotally, a stepwise clamping method has sometimes been preferred to straightforward clamping to train the sphincter of Oddi in the papilla of Vater after decompression through the drainage tube following LT. The preference for the stepwise method is due to concerns that straightforward clamping may lead to dysfunction of the sphincter of Oddi after long-term decompression through the stent tube. However, it is not known whether stepwise clamping truly yields a better outcome, and there has been no report examining this matter in LT.

We investigated 40 LDLT patients who were randomly allocated to two groups in which different methods were used for clamping the biliary drainage tube.

Methods

Patients

Of 66 patients in whom we performed liver transplantations between May 2006 and October 2009, 65 were adult-to-adult LDLTs. Of these 65, 40 patients who underwent duct-to-duct biliary reconstruction with a tube splint at the anastomotic site and survived beyond 3 months were included in this study. This prospective randomized control study was conducted with the permission of the institutional ethics committee. Six ABO-incompatible patients

received a single dose of rituximab 1 week prior to the LDLT [4].

Biliary drainage tube placement

As reported previously, we used a polyvinyl chloride tube of 2-mm diameter, which was originally used for retrograde transhepatic biliary drainage, for our LDLT patients [3]. The tube was equipped with a malleable metallic dull-tipped splint at one end. Prior to the performance of duct-to-duct biliary anastomosis, the metallic splint of the tube was inserted from the lumen of the recipient's side of the hepatic duct and externalized through the common bile duct above the upper edge of the duodenum. Subsequently, duct-to-duct anastomosis was performed with interrupted sutures of 6-0 polydioxanone, and the tube was placed inside the graft intrahepatic bile duct for decompression and splinting. After the tube placement, the externalized site of the common bile duct was treated with purse-string sutures of 6-0 polydioxanone. Ductoplasty was performed in 4 patients with a right lobe graft; in 3 of these patients two tubes were placed, one in the anterior and one in the posterior branches of the bile duct. In the other patient with a right lobe graft, two tubes were placed when anterior and posterior branches of the bile ducts were too distant to perform ductoplasty.

Groups

When the serum levels of total bilirubin were lower than 5 mg/dl, and negativity for any biliary complications (leakage or severe stricture) and a good passage of contrast media to the duodenum were confirmed by fluoroscopic study, an attempt to clamp the biliary drainage tube was initiated 1 day after the fluoroscopic study. The following two methods were used for the clamping: for stepwise clamping ($n = 20$), the drain tube was clamped for 3 h on day 1, 6 h on day 2, 12 h on day 3, and 24 h per day thereafter. After each temporary clamping, the biliary drainage tube was opened and externally drained. For the straightforward clamping ($n = 20$), the drain tube was clamped and remained closed.

After the clamping, liver function tests (T. Bil: total bilirubin, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma glutamyl transpeptidase) were performed on days 1 and 3. During the clamping period, the patients continued to eat hospital meals three times a day.

Statistics

All data were expressed as median values with ranges. Statistical analysis was performed using the Mann–

Table 1 Patient characteristics and liver function tests after the clamping

| | Stepwise ($n = 20$) | Straightforward ($n = 20$) | |
|---|--------------------------|---------------------------------|------|
| Age (years) | 56 (31–67) | 57 (33–68) | n.s. |
| Gender (M:F) | 13:7 | 13:7 | n.s. |
| Graft type (right-side graft:left-lobe graft) | 10:10 | 10:10 | n.s. |
| Bile ductoplasty | 3 | 1 | n.s. |
| Double tubes | 3 | 0 | n.s. |
| ABO-incompatible | 1 (5%) | 5 (20%) | n.s. |
| Starting day of the clamping | 22 (12–54) | 29 (9–59) | n.s. |
| T. Bil before clamping (mg/dL) | 1.9 (0.6–5.6) | 2.0 (0.6–11.1) | n.s. |
| After 1 day | 1.9 (0.5–5.4) | 1.8 (0.7–9.6) | n.s. |
| After 3 days | 1.5 (0.5–4.6) | 1.5 (0.4–7.2) | n.s. |
| ALT before clamping (IU/L) | 73 (24–177) | 89 (5–537) | n.s. |
| After 1 day | 67 (21–178) | 80 (7–567) | n.s. |
| After 3 days | 60 (16–177) | 81 (8–542) | n.s. |
| ALP before clamping (IU/L) | 377 (115–1,744) | 369 (176–1,100) | n.s. |
| After 1 day | 382 (136–1,736) | 377 (107–1,260) | n.s. |
| After 3 days | 345 (138–1,698) | 380 (169–1,410) | n.s. |
| GGT before clamping (IU/L) | 94 (13–368) | 100.5 (17–538) | n.s. |
| After 1 day | 113 (17–358) | 150 (16–549) | n.s. |
| After 3 days | 94.5 (14–365) | 100 (16–577) | n.s. |

Numbers in parentheses are ranges, unless otherwise indicated. *n.s.* not significant, *T. Bil* total bilirubin, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *GGT* gamma glutamyl transpeptidase

Whitney *U*-test for continuous values. Statistical significance was defined as a *p* value of <0.05. The StatView 5.0 software program (Abacus Concepts, Berkeley, CA, USA) was used for all statistical analyses.

Results

Table 1 shows the characteristics of the patients in the study. There were no statistically significant differences in age, gender, graft type, the starting day of clamping after LDLT, or ABO incompatibility between the groups.

At the time of the clamping, there were also no significant differences between the groups in the serum levels of T. Bil, ALT, ALP, and GGT. After each type of clamping of the biliary drainage tube, there were no significant differences between the groups in the serum levels of total bilirubin, AST, ALP, or GGT on days 1 and 3. There was no clamping failure in either of the groups.

Discussion

In the present study, we demonstrated that there were no differences in the patient outcomes after using the stepwise versus the straightforward clamping method for the biliary drainage tube after LDLT.

Biliary splinting plays an important role in LDLT, as the rate of biliary complications is higher in LDLT than in deceased-donor whole LT [1, 2]. We generally use a 2-mm tube for stenting at the biliary anastomosis, externalize it through the lower common bile duct, and fistulize it using the duodenal serosa [3]. The safety of the two-step procedure for removal of the splint tube was reported previously by our group [3]. In order to clarify the effects of the stepwise clamping method, we performed the present prospective study.

In our patients, there were no differences between the groups in the distribution of graft type, i.e., right lobe grafts, right posterior grafts, and left lobe grafts. After the clamping, we observed no differences between the outcomes in the patients treated using the two different clamping methods. In addition, in our subgroup analysis of graft type within each group, there were no significant differences in any of the parameters. Moreover, ABO-incompatible patients did not show any additional response after clamping of the biliary drainage tube, regardless of the clamping method used.

In one patient, we started to clamp the tube when the level of total serum bilirubin was still more than 5 mg/dl because of a lack of any biliary complications at 2 months after LDLT. However, there was no increase in any of the examined parameters in this patient in the straightforward clamping group.

Studies on the duration of clamping procedures have been performed only in the area of total knee arthroplasty [5–8]. In one of these studies, a reduction of blood loss was confirmed when 1-h clamping was applied as compared to a 4-h clamping method [5]. However, there has been no

previous report describing the clamping method or duration of use for a biliary drainage system; therefore, even specialists in this field sometimes adopt the conventional stepwise method after LDLT.

In conclusion, we performed a randomized control study to examine differences arising due to the use of different clamping methods. Our results indicate that the straightforward clamping method could be a simple and reasonable method to successfully close biliary drainage tubes after LDLT.

References

1. Ishiko T, Egawa H, Kasahara M, et al. Duct-to-duct biliary reconstruction in living donor liver transplantation utilizing right lobe graft. *Ann Surg.* 2002;236:235–40.
2. Sakamoto S, Egawa H, Ogawa K, et al. The technical pitfalls of duct-to-duct biliary reconstruction in pediatric living-donor left-lobe liver transplantation: the impact of stent placement. *Pediatr Transpl.* 2008;12:661–5.
3. Eguchi S, Takatsuki M, Hidaka M, Tajima Y, Kanematsu T. Two-step biliary external stent removal after living donor liver transplantation. *Transpl Int.* 2008;21:531–3.
4. Egawa H, Teramukai S, Haga H, Tanabe M, Fukushima M, Shimazu M. Present status of ABO-incompatible living donor liver transplantation in Japan. *Hepatology.* 2008;47:143–52.
5. Madadi F, Mehrvarz AS, Madadi F, Boreiri M, Abachizadeh K, Ershadi A. Comparison of drain clamp after bilateral total knee arthroplasty. *J Knee Surg.* 2010;23:215–21.
6. Ryu J, Sakamoto A, Honda T, Saito S. The postoperative drain-clamping method for hemostasis in total knee arthroplasty. Reducing postoperative bleeding in total knee arthroplasty. *Bull Hosp Jt Dis.* 1997;56:251–4.
7. Yamada K, Imaizumi T, Uemura M, Takada N, Kim Y, et al. Comparison between 1-hour and 24-hour drain clamping using diluted epinephrine solution after total knee arthroplasty. *J Arthroplasty.* 2001;16:458–62.
8. Stucinskas J, Tarasevicius S, Cebatorius A, Robertsson O, Smailys A, Wingstrand H. Conventional drainage versus four hour clamping drainage after total knee arthroplasty in severe osteoarthritis: a prospective, randomized trial. *Int Orthop.* 2009;33:1275–8.

Prevention of gastric stasis by omentum patching after living donor left hepatectomy

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Abstract Among 137 living liver donors who underwent partial hepatectomy between August 1997 and November 2010, 58 donated the left lobe of their liver, with or without the caudate lobe. Gastric stasis developed after surgery in 4 (7 %) of these 58 donors (Fig. 1); possibly because of dislocation of the stomach after hepatectomy and adhesion between the stomach and the cut surface of the liver. This complication is specific to left hepatectomy [1] and although not life-threatening, it is symptomatic and requires endoscopic or surgical intervention. We describe our surgical technic designed to prevent this complication.

Keywords Liver transplantation · Living donor · Omentum

Surgical procedures (Fig. 2)

After left hepatectomy, there is a large cavity between the stomach and the cut surface of the liver (Fig. 2a). A closed suction drain is generally placed along the cut surface via the dorsal route of the hepatoduodenal ligament. Our method involves stretching the omentum fully (Fig. 2b) into this space, covering the hepatoduodenal ligament and the cut surface of the liver (Fig. 2c), ensuring that the stomach and transverse colon are left in their natural positions. We simply leave the omentum in place without suturing (Fig. 2d). Patients with gastric stasis vomit

frequently because their stomach is enlarged, as can be seen on abdominal X-ray and/or computed tomography images (Fig. 1). Computed tomography is performed routinely 1 month after surgery, mainly to check the regeneration of the liver.

We performed omental patching in the most recent 45 of the 58 donors who underwent left partial hepatectomy. The incidence of gastric stasis decreased significantly from 23 % (3/13) in the first 13 patients to 2 % (1/45) in the last 45 ($P < 0.05$; Fisher's test). Computed tomography after surgery confirmed that the omentum was still in place between the stomach and the liver (Fig. 3a), preventing adhesion between them in all except one patient, in whom gastric stasis was possibly caused by dislocation of the omentum. All 3 of the former 13 patients with gastric stasis after surgery without omentum patching were observed to have tight adhesion between the stomach and the cut surface of the liver (Fig. 3b).

Gastric stasis is not life-threatening, but it impairs the quality of life of living liver donors. In left hepatectomy, the stomach is twisted and falls into the space after the liver lobe is removed. This leads to adhesion between the stomach and the cut surface of the liver. None of the 62 patients who underwent right hepatectomy during the same period in this series suffered any gastric stasis. Although all four of our patients who suffered gastric stasis are now doing well, three required endoscopic repair, and one required surgical adhesiolysis. There are few studies on the prevention of gastric stasis after left hepatectomy. Yoshida et al. [2] proposed a procedure for fixing the greater omentum to the peritoneum to prevent the stomach from falling into the space after hepatectomy. We devised omentum patching because it is simple and requires no artificial materials. A sodium hyaluronate and carboxymethylcellulose membrane was recently introduced as an

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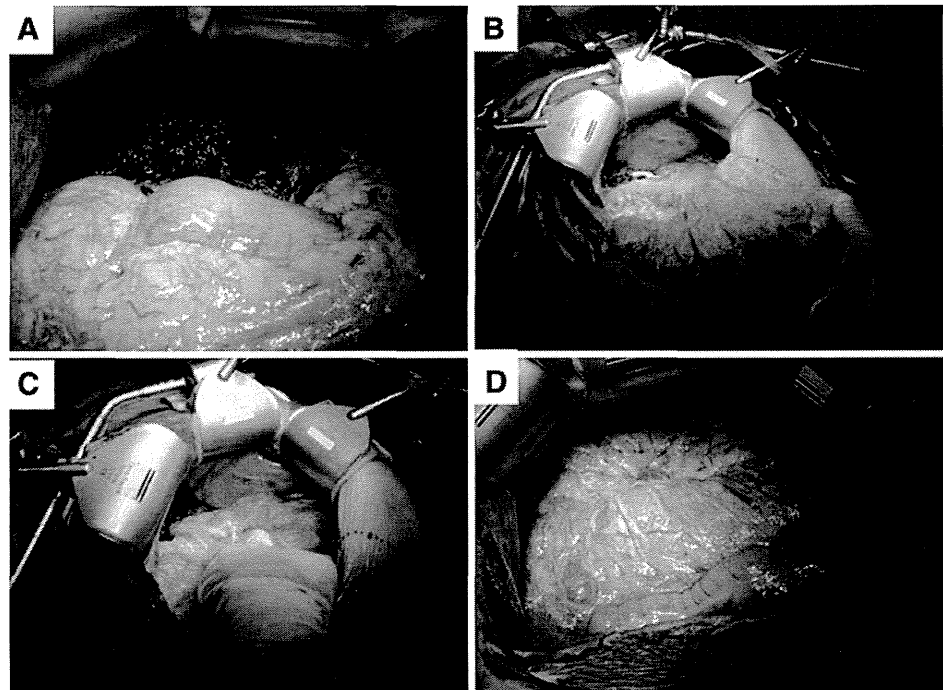
Fig. 1 Gastric stasis after living donor left hepatectomy. Fluorescent imaging study shows an enlarged stomach with no passage of radiofluorescence through the pylorus

effective material to prevent bowel obstructions being caused by adhesions [3, 4], but it is not clear whether it can be used to prevent adhesions between the cut surface of the liver and the stomach. Besides the omentum, another intra-abdominal material that could possibly be used is intestine, but this might lead to bowel obstruction due to adhesion. We simply left the omentum without any plasty in the

space between the stomach and the cut surface of the liver, and without sutures. Even though it was not fixed, computed tomography confirmed that the omentum remained in place between the stomach and the liver in most of the patients. The omentum is used widely to prevent or treat various morbidities, including anastomotic leakage of the colon [5], perforation of a duodenal ulcer [6], hepatic hydatid cyst [7], and in some thoracic surgery [8]. It is generally used with some kind of plasty, but we simply placed it over the area without any plasty or sutures, and thus named the procedure as “omentum patching”. This procedure cannot be applied if the omentum is too small to cover the cut surface of the liver, or if there are intra-abdominal adhesions involving the omentum from prior laparotomy. In our series, omentum patching was carried out easily in all patients, except for one who had previously undergone colectomy. We believe that the vast majority of living liver donors are candidates for omentum patching at the time of hepatectomy because they are healthy volunteers. This procedure is also useful for patients undergoing left hepatectomy for neoplasms, but it is more applicable in living donor hepatectomy, in which any complications, even minor ones, should be avoided.

One possible disadvantage of this procedure is that it may leave the person susceptible to severe peritonitis if intra-abdominal inflammation, such as appendicitis, occurs after surgery, because the general functions of the omentum include migration, covering, adhesion, and mending the absorption against peritoneal injury or infection. None of our patients have experienced any such adverse events

Fig. 2 Surgical procedure for omentum patching. There is a large cavity between the stomach and the cut surface of the liver (a). The omentum is fully stretched (b) and placed over the hepatoduodenal ligament and the cut surface of the liver (c). The omentum is left in place without sutures (d)



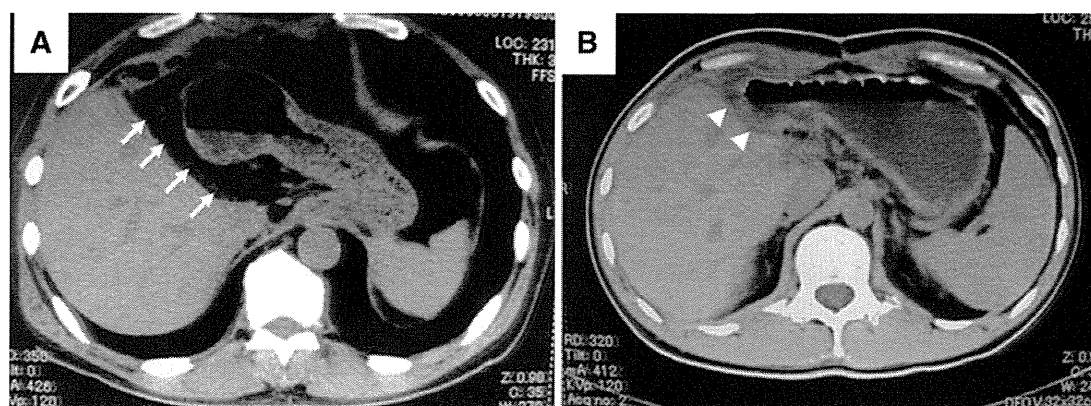


Fig. 3 Computed tomography scan after surgery with (a) and without (b) omentum patching. After omentum patching, the omentum remains in place between the stomach and the cut surface of the

liver (arrows, a), whereas without omentum patching, there are tight adhesions in a person suffering from gastric stasis (arrowheads, b)

within a median follow-up period of 16 months (range 1–42 months). Another possible cause of adhesion between the stomach and the cut surface of the liver is bile leakage. Thus, it is essential to cut the bile duct at an adequate point [9]. There were no cases of bile leakage causing tight adhesion in our series, as we cut the bile duct at the optimal cutting point during donor surgery using C-arm cholangiography [10].

In conclusion, although a randomized study should be done, the findings of this series demonstrate that omentum patching prevents gastric stasis after living donor left hepatectomy.

References

1. Taketomi A, Kayashima H, Soejima Y, Yoshizumi T, Uchiyama H, Ikegami T, et al. Donor risk in adult-to-adult living donor liver transplantation: impact of left lobe graft. *Transplantation*. 2009;87:445–50.
2. Yoshida H, Mamada Y, Tani N, Mizuguchi Y, Shimizu T, Kakinuma D, et al. Fixation of the greater omentum for prevention of delayed gastric emptying after left hepatectomy with lymphadenectomy for cholangiocarcinoma. *J Hepatobiliary Pancreat Surg*. 2007;14:392–6.
3. Beck DE, Cohen Z, Fleshman JW, Kaufman HS, van Goor H, Wolff BG, Adhesion Study Group Steering Committee. A prospective, randomized, multicenter, controlled study of the safety of Sefrafil™ adhesion barrier in abdominopelvic surgery of the intestine. *Dis Colon Rectum*. 2003;46:1310–9.
4. Fazio VW, Cohen Z, Fleshman JW, van Goor H, Bauer JJ, Wolff BG, et al. Reduction in adhesive small-bowel obstruction by Sefrafil™ adhesion barrier after intestinal resection. *Dis Colon Rectum*. 2006;49:1–11.
5. Hao XY, Yang KH, Guo TK, Ma B, Tian JH, Li HL. Omentoplasty in the prevention of anastomotic leakage after colorectal resection: a meta-analysis. *Int J Colorectal Dis*. 2008;23:1159–65.
6. Gypen BJ, Hubens GJ, Hartman V, Balliu L, Chapelle TC, Vaneerdeweg W. Perforated duodenal ulcer after laparoscopic gastric bypass. *Obes Surg*. 2008;18:1644–6.
7. Gourgoutis S, Stratopoulos C, Moustafellos P, Dimopoulos N, Papaxoinis G, Vougas V, et al. Surgical techniques and treatment for hepatic hydatid cysts. *Surg Today*. 2007;37:389–95.
8. Nosotti M, Cioffi U, De Simone M, Mendogni P, Palleschi A, Rosso L, et al. Omentoplasty and thoracoplasty for treating postpneumectomy bronchopleural fistula in a patient previously submitted to aortic prosthesis implantation. *J Cardiothorac Surg*. 2009;4:38.
9. Igami T, Yokoyama Y, Nishio H, Ebata T, Sugawara G, Senda Y, et al. A left hepatectomy and caudate lobectomy combined resection of the ventral segment of the right anterior sector for hilar cholangiocarcinoma—the efficacy of PVE (portal vein embolization) in identifying the hepatic subsegment: report of a case. *Surg Today*. 2009;39:628–32.
10. Takatsuki M, Eguchi S, Yamanouchi K, Hidaka M, Soyama A, Kanematsu T. Technical refinements of bile duct division in living donor liver surgery. *J Hepatobiliary Pancreat Sci*. 2011;18:170–5.



Standardized Less Invasive Living Donor Hemihepatectomy Using the Hybrid Method Through a Short Upper Midline Incision

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ABSTRACT

Background. Recently, applications of less invasive liver surgery in living donor hepatectomy (LDH) have been reported. The objective of this study was to evaluate the safety and efficacy of a hybrid method with a midline incision for LDH.

Methods. Hemihepatectomy using the hybrid method was performed in the fifteen most recent among 150 living donors who underwent surgery between 1997 and August 2011. Six donors underwent right hemihepatectomy and 9 underwent left hemihepatectomy. An 8-cm subxiphoid midline incision was created for hand assistance during liver mobilization and graft extraction. After sufficient mobilization of the liver, the hand-assist/extraction incision was extended to 12 cm for the right hemihepatectomy and 10 cm for a left hemihepatectomy. Encircling the hepatic veins and hilar dissection were performed under direct vision. Parenchymal transection was performed with the liver hanging maneuver. Bile duct division was performed after visualizing the planned transection point by encircling the bile duct using a radiopaque marker filament under real-time C-arm cholangiography.

Results. All procedures were completed without any extra subcostal incision. All grafts were safely extracted through the 10–12-cm upper midline incision without mechanical injury. No donors required an allogeneic transfusion; all of them have returned to their preoperative activity levels.

Conclusion. LDH by the hybrid method with a short upper midline incision is a safe procedure.

DONOR safety is of the utmost importance for living donor liver transplantation (LDLT). Recently, the application of less invasive liver surgery has been reported during living donor hepatectomy (LDH).^{1,2} We have adopted laparoscopy-assisted donor hepatectomy through a short upper midline incision with hilar dissection and parenchymal transection under direct vision as a new LDH method. For this procedure, we have applied useful techniques that we established for the conventional open LDH. Herein we have described the procedure for laparoscopic-assisted donor hepatectomy at our institute, providing an evaluation of its safety and efficacy using a short midline incision for LDH.

PATIENTS AND METHODS

Between 1997 and August 2011, we performed 150 LDLT, including the most recent 15 donors who underwent a laparoscopy-

assisted donor hepatectomy, which consisted of a 2-phase laparoscopic procedure and an open procedure, the hybrid technique.³ Six donors underwent a right and 9 underwent a left hemihepatectomy using the laparoscopy-assisted hybrid procedure.

Right Hemihepatectomy

The donor was placed in the supine position with abducted arms. An 8-cm subxiphoid midline incision was created for hand assistance during liver mobilization and graft extraction, using a GelPort handport device (Applied Medical, Rancho Santa Margarita, Calif, United States). Pneumoperitoneum (CO₂ at 8 mm Hg)

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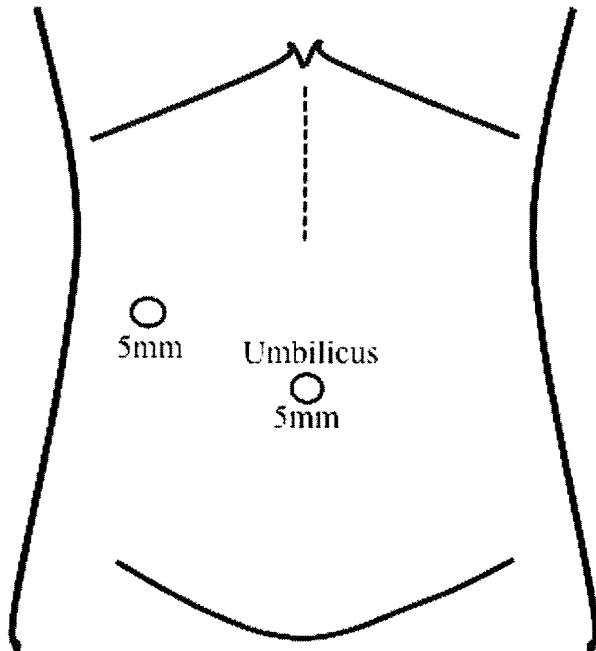


Fig 1. Trocar placement for laparoscopy-assisted donor hemihepatectomy. A 5-mm camera port was placed at the umbilicus. An 8-cm upper midline incision was made for setting the Gel Port handport device for hand-assisted mobilization of the liver.

was established through a 5-mm umbilical camera port. Once the liver was visualized, we placed an additional 5-mm port at the right flank or through the GelPort (Fig 1). The first assistant, who stood on the left side of the donor, manipulated the liver for the mobilization with hand-assistance through the hand port. Through the right flank port, the surgeon, who stood on the right side of the donor, used hook-type electrocautery to divide the ligaments and perform the dissection to sufficiently mobilize the liver until reaching the lateral wall of the inferior vena cava. At this point, we removed the hand port and the other ports. The midline incision was then extended to 12 cm for the subsequent open procedure. To provide sufficient exposure, the short incision was retracted with an Omni-Tract (Omni-Tract Surgical, St. Paul, Minn, United States). After exposing the inferior vena cava, we divided the short hepatic and encircling veins under direct vision.

After encircling the right hepatic vein, a Penrose drain was passed around the hepatic vein for the liver-hanging maneuver. As

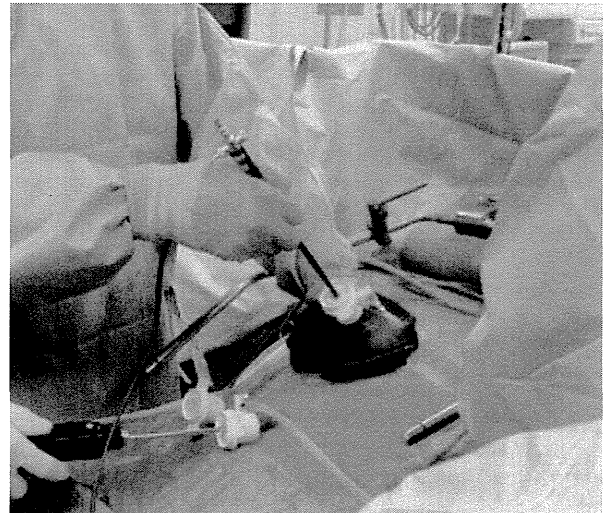


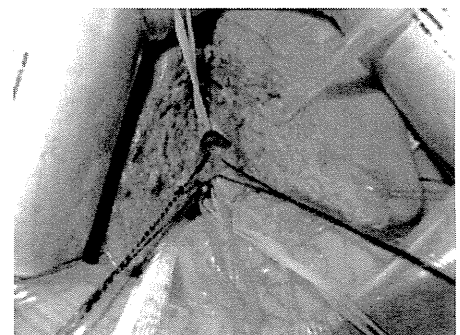
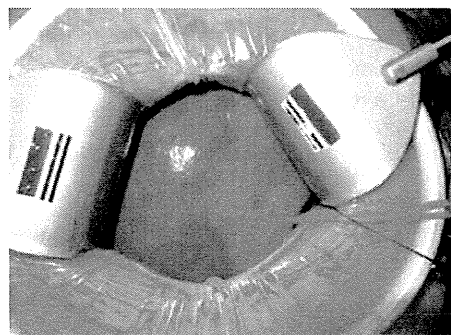
Fig 3. For dissection of the left triangular ligament and left side of the coronal ligament, a 5-mm trocar is placed through the GelPort hand port device.

a result of the sufficient mobilization of the right lobe and using the liver-hanging maneuver, the transection line came just beneath the upper midline incision (Fig 2). A parenchymal transection was performed using the CUSA (Integra Life Sciences, Plainsboro, NJ, USA) and Tissue Link dissecting sealers (Salient Surgical Technologies, Portsmouth, NH, United States), which is the so-called two-surgeon technique.⁴ We performed bile duct division after visualizing the planned transection point by encircling the bile duct using a radiopaque marker filament under real-time C-arm cholangiography.⁵ The resected right lobe was retrieved through a short upper midline incision.

Left Hemihepatectomy

The donor position and settings of the laparoscopic procedure were the same as the right hemihepatectomy. In the same manner as during the right hemihepatectomy, the right lobe of the liver was sufficiently mobilized during the left hemihepatectomy. Otherwise, the transection line along the Cantlie line was not safely positioned under direct vision through the short upper midline incision. To dissect the left triangular ligament and the left side of the coronal ligament, a 5-mm port was placed through the GelPort (Fig 3).

Fig 2. The appearance of the demarcation line after the clamping of the right hepatic artery and right branch of the portal vein. After the mobilization of the right liver, the transection line comes just beneath the short upper midline incision after performing the liver-hanging maneuver.



Intraoperative and postoperative outcomes

The median length of the operation and blood loss were 456 minutes (range, 328–581) and 520 g (range, 230–1000), respectively. The donors were transferred to the surgical intensive care unit for an overnight stay. On postoperative day 1, they were transferred to the nursing ward with surgical site pain controlled by parenteral analgesics. Donor recovery was uneventful except for 1 donor who required a relaparotomy to remove a portal venous thrombus. Serum chemistry findings were similar to those of our open donors (data not shown). All donors fully recovered, returning to their previous activities. On follow-up as outpatients, wound healing was favorable in all donors (Fig 4).

DISCUSSION

Herein we have described 15 donor laparoscopic-assisted hemihepatectomies performed through a short upper midline incision. Koffron et al reported the first laparoscopic, hand-assisted living donor right hepatic lobectomy using an upper midline incision.¹ In laparoscopy-assisted LDH at

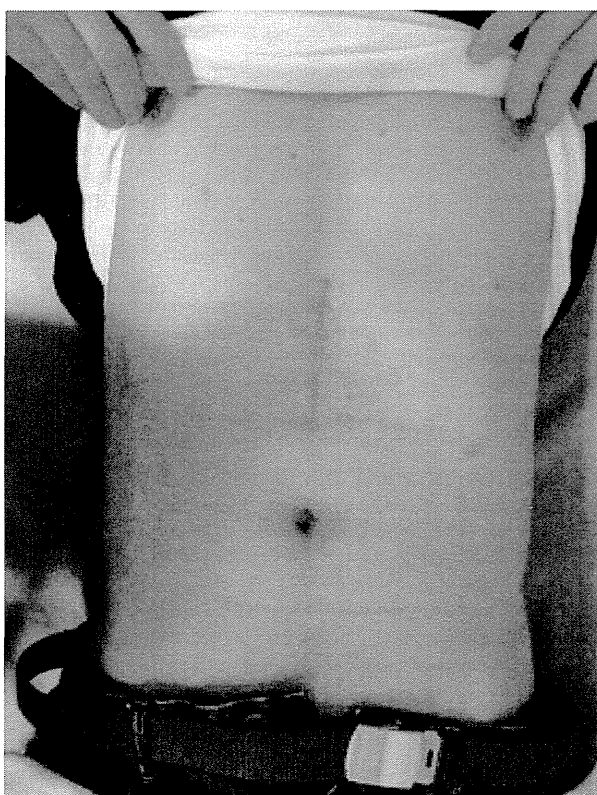


Fig 4. The wound left by the upper midline 10-cm incision 1 month after the left hemihepatectomy. The wound from the umbilical port was nearly invisible.

our institute, besides the procedures that Koffron et al reported, we have introduced other techniques that we had already established for open procedures.

We consider dividing the short hepatic veins and the subsequent encircling of the right hepatic vein or the common trunk of the middle hepatic vein and left hepatic vein can be more securely performed under direct vision compared with a laparoscopic procedure. Minimizing blood loss is the most important element of laparoscopic liver surgery. Because the retrohepatic vena cava and the hepatic veins can be controlled for urgent extensive bleeding, dissecting those vessels under direct vision seems to be a reasonable approach. Once the right lobe is mobilized, the liver can be rotated to the left of the midline for retraction; therefore, the surgeon can easily approach the inferior vena cava and the right hepatic vein even through the mini-laparotomy with a short upper midline incision. The 2-surgeon technique that is performed during parenchymal transection can also be conducted during open procedures using the liver-hanging maneuver, which brings the transection line to just beneath the upper midline incision while pulling up the liver.⁴ As a result, parenchymal transection can be completed through a 10–12-cm upper midline incision without stress to the surgeons.

Visualizing the planned transection point by encircling the bile duct using a radiopaque marker filament contributed to avoiding biliary complications when we divided the bile duct in the smaller working space compared with the open procedure.⁵ Depending on the type of graft, we used different lengths of incisions: 12 cm for safe retrieval of a right and 10 cm for a left lobe graft.

In conclusion, LDH by the hybrid method via an upper midline incision was a safe procedure using the combination of hand-assistance and techniques that have been established for open donor surgery.

REFERENCES

1. Koffron AJ, Kung R, Baker T, et al: Laparoscopic-assisted right lobe donor hepatectomy. *Am J Transplant* 6:2522, 2006
2. Wakabayashi G, Nitta H, Takahara T, et al: Standardization of basic skills for laparoscopic liver surgery towards laparoscopic donor hepatectomy. *J Hepatobiliary Pancreat Surg* 16:439, 2009
3. Buell JF, Cherqui D, Geller DA, et al: World Consensus Conference on Laparoscopic Surgery. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. *Ann Surg* 250:825, 2009
4. Takatsuki M, Eguchi S, Yamanouchi K, et al: Two-surgeon technique using saline-linked electric cautery and ultrasonic surgical aspirator in living donor hepatectomy: its safety and efficacy. *Am J Surg* 197:e25, 2009
5. Takatsuki M, Eguchi S, Yamanouchi K, et al: Technical refinements of bile duct division in living donor liver surgery. *J Hepatobiliary Pancreat Sci* 18:170, 2011

Intraoperative portal venous pressure and long-term outcome after curative resection for hepatocellular carcinoma

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Background: Outcomes of liver resection for hepatocellular carcinoma (HCC) have improved owing to better surgical techniques and patient selection. Portal hypertension may influence outcome but the preoperative definition and role of portal hypertension are far from clear. The aim of this study was to elucidate the influence of portal venous pressure (PVP) measured directly during surgery on outcomes of liver resection in patients with HCC.

Methods: Patients who had resection of HCC between 1997 and 2009, and who underwent direct measurement of PVP immediately after laparotomy were enrolled. These patients were divided into groups with high (at least 20 cmH₂O) and low (less than 20 cmH₂O) PVP. The influence of PVP on overall and recurrence-free survival was analysed and prognostic factors were identified.

Results: A total of 177 patients were enrolled, 129 in the low-PVP group and 48 in the high-PVP group. The 5-year overall survival rate (63.7 versus 31 per cent; $P < 0.001$) and recurrence-free survival rate (52.5 versus 12 per cent; $P < 0.001$) were significantly higher in patients with low PVP. In multivariable analysis, two or more tumours, tumour diameter at least 5 cm, high PVP, grade B liver damage and Hepatic Activity Index (HAI) grade 7 or more were significant predictors of poorer survival after liver resection. Two or more tumours, tumour diameter at least 5 cm and HAI grade 7 or more were significant predictors of poorer recurrence-free survival.

Conclusion: High PVP was associated with poor long-term outcome after liver resection for HCC.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide¹. Outcomes of liver resection for HCC have improved greatly in recent years because of improved surgical techniques and better perioperative management^{2,3}. Adequate estimation of preoperative liver function and tailoring the extent of hepatectomy based on liver function have reduced postoperative mortality and morbidity rates²⁻⁴.

The degree of portal hypertension probably reflects the severity of fibrosis in patients with liver cirrhosis. Patients with cirrhosis often have portal hypertension before surgery, and currently are not candidates for liver resection, especially major hepatectomy, according to North American and European guidelines^{5,6}. Several reports have shown an association between portal

hypertension estimated before surgery and the prognosis of HCC^{7,8}. Major hepatic resection increases portal venous pressure (PVP) in cirrhotic and non-cirrhotic livers. This increase in PVP after hepatectomy, however, does not seem to have a direct effect on early postoperative morbidity and mortality⁹. On the other hand, directly measured high PVP during hepatectomy has been associated with postoperative complications in patients with cirrhosis and HCC¹⁰.

The aim of the present study was to clarify whether PVP reflects the prognosis of patients with HCC after hepatic resection, and to identify factors affecting recurrence and survival.

Methods

All patients with HCC who underwent curative hepatic resection between January 1997 and December 2009 in the

Department of Surgery, Nagasaki University Hospital, and in whom PVP was measured, were eligible for the study. Curative resection was defined as any operation in which all tumours were resected macroscopically.

Hepatic resection was performed based on preoperative tumour staging and liver function tests. The selection for minor resection (partial hepatectomy or segmentectomy) or major resection (here defined as bisegmentectomy and lobectomy) was based on the location and diameter of HCC and liver function tests⁹. Tumour staging included preoperative ultrasonography, multidetector computed tomography (CT) and magnetic resonance imaging (MRI) in all patients. Preoperative liver function was assessed by liver function tests, indocyanine green retention rate at 15 min (ICG-R15), liver scintigraphy represented by the liver to liver plus heart ratio at 15 min (LHL15) after ^{99m}Tc-labelled galactosyl sialyl albumin loading, and Child–Pugh classification.

Patient data collected before surgery included age, sex, virus status, platelet count, prothrombin time, albumin, total bilirubin, alanine aminotransferase (ALT), Child–Pugh grade, liver damage defined by the Liver Cancer Study Group of Japan¹¹, ICG-R15 and LHL15.

Intraoperative PVP measurement was performed as described previously^{9,10}. Briefly, a catheter was inserted into a jejunal mesenteric vein around 100–120 cm from Treitz's ligament before liver mobilization and resection. PVP was then measured using a water pressure gauge with saline. Patients with a history of upper abdominal surgery and mesenteric membrane adhesions were excluded because intubation could not be done easily after laparotomy. A high PVP was defined as a pressure of at least 20 cmH₂O^{9,10}. Pressure over 15 mmHg was considered an indicator to avoid small-for-size graft syndrome after liver transplantation. Generally, a PVP of 15 mmHg was taken to be equal to 20 cmH₂O (conversion factor 1.36)¹². Patients were divided into groups with high (at least 20.0 cmH₂O) and low (below 20.0 cmH₂O) PVP at the time of surgery. Liver dysfunction was defined by hyperbilirubinaemia, severe ascites, lower prothrombin time and raised sustained levels in liver function tests after hepatectomy.

Postoperative follow-up included measurement of serum α -fetoprotein (AFP) and serum protein induced by vitamin K absence II (PIVK_{II}) levels, and ultrasonography, CT or MRI every 2 or 3 months. If indicated, chest CT or bone scintigraphy were performed. If tumour recurrence was found, the optimal treatment (transarterial chemoembolization for intrahepatic multiple recurrence, radiofrequency ablation for single small recurrence, repeat hepatectomy for single intrahepatic recurrence) was selected for patients with preserved liver function.

Statistical analysis

Preoperative clinical data in the high- and low-PVP groups were compared, including age, sex, virus status, Child–Pugh classification, liver damage, ICG-R15, LHL15, platelet count, prothrombin time, serum albumin, total bilirubin, ALT, AFP and PIVK_{II}, and pathological data, including number and diameter of tumours, vascular invasion, liver inflammation and fibrosis graded using the Hepatic Activity Index (HAI)¹³. Clinical and pathological factors related to the presence of high PVP were compared by means of the Mann–Whitney *U* test and χ^2 test. Survival was analysed from the day of surgery to most recent follow-up. Survival and recurrence-free survival rates were determined by the Kaplan–Meier method and compared using the log rank test. To identify prognostic factors for survival and recurrence, 14 clinical and pathological variables were included in univariable and multivariable analyses using the Cox proportional hazard model. *P* < 0.050 was considered statistically significant. Statistical analyses were done using SPSS[®] version 18.0 (SPSS, Tokyo, Japan).

Results

A total of 177 patients were included in the analysis, with a median age of 65 (range 20–81) years; 83.1 per cent were men (Table 1). Forty-seven patients (26.6 per cent) were seropositive for hepatitis B antigen (HBs-Ag), three (1.7 per cent) were seropositive for HBs-Ag and hepatitis C antibody (HCV-Ab), 84 (47.5 per cent) were seropositive for HCV-Ab, and 43 (24.3 per cent) were seronegative for both HBs-Ag and HCV-Ab.

Forty-eight patients had high PVP and the remaining 129 had low PVP. Patients with high PVP had a lower platelet count, a lower prothrombin time, lower albumin level, higher ALT concentration, higher Child–Pugh grade, higher grade of liver damage, higher ICG-R15, lower LHL15 and higher AFP level; solitary tumours were less common in this group, resulting in fewer major hepatectomies, and a higher HAI grade and stage (Table 1). Eighteen (38 per cent) of 48 patients in the high-PVP group had a platelet count of less than $10 \times 10^4/\text{mm}^3$ compared with 13 (10.1 per cent) of 129 in the low-PVP group.

Twenty patients (42 per cent) in the high-PVP group developed complications after hepatectomy, including ascites in eight (17 per cent), pleural effusion in eight (17 per cent) and infectious disease in eight (17 per cent). Fifty-four patients (41.9 per cent) with low PVP developed complications, with ascites in 18 (14.0 per cent), pleural effusion in 23 (17.8 per cent) and infectious disease in nine

Table 1 Clinical characteristics of patients with high or low portal venous pressure undergoing hepatectomy for hepatocellular carcinoma

| | High PVP (≥ 20 cmH ₂ O) (n = 48) | Low PVP (<20 cmH ₂ O) (n = 129) | P† |
|---|---|--|--------|
| Age (years)* | 63 (43–78) | 66 (20–81) | 0.162‡ |
| Sex ratio (M:F) | 40:8 | 107:22 | 0.856 |
| Aetiology | | | 0.347 |
| Hepatitis B | 14 (29) | 33 (25.6) | |
| Hepatitis C | 26 (54) | 58 (45.0) | |
| Hepatitis B + C | 1 (2) | 2 (1.6) | |
| Hepatitis-negative | 7 (15) | 36 (27.9) | |
| Platelet count ($\times 10^4/\text{mm}^3$)* | 11.8 (4.1–35.6) | 15.9 (2.6–47.0) | 0.001‡ |
| Prothrombin time (%)* | 84 (63–105) | 91 (54–122) | 0.002‡ |
| Albumin (g/dl)* | 3.8 (2.5–4.7) | 4.0 (2.8–4.8) | 0.001‡ |
| Total bilirubin (mg/dl)* | 0.9 (0.4–4.8) | 0.7 (0.3–2.4) | 0.060‡ |
| ALT (units)* | 55.5 (18–190) | 34.5 (7–222) | 0.002‡ |
| Child–Pugh grade | | | 0.004 |
| A | 38 (79) | 122 (94.6) | |
| B | 10 (21) | 7 (5.4) | |
| Liver damage grade | | | 0.001 |
| A | 30 (63) | 112 (86.8) | |
| B | 18 (37) | 17 (13.2) | |
| ICG-R15 (%)* | 18 (3–39) | 11 (1–40) | 0.004‡ |
| LHL15* | 0.89 (0.77–0.96) | 0.93 (0.61–0.97) | 0.001‡ |
| AFP (ng/ml)* | 47.5 (4.2–454.300) | 13.1 (1.2–151.367) | 0.030‡ |
| PIVKaII (mAU/ml)* | 73 (21–10.173) | 133 (2–60.380) | 0.522‡ |
| Tumour diameter (cm)* | 2.9 (1.0–13.0) | 4.0 (0.5–17.0) | 0.080‡ |
| Solitary tumour | 29 (60) | 101 (78.3) | 0.016 |
| Type of hepatectomy | | | 0.001 |
| Minor | 41 (85) | 76 (58.9) | |
| Major | 7 (15) | 53 (31.1) | |
| Vascular invasion | 10 (21) | 40 (31.0) | 0.207 |
| HAI* | | | |
| Grade | 9.1 (3–13) | 4.8 (1–13) | 0.001‡ |
| Stage | 3.8 (2–4) | 2.1 (0–4) | 0.001‡ |

Values in parentheses are percentages unless indicated otherwise; *values are median (range). PVP, portal venous pressure; ALT, alanine aminotransferase; ICG-R15, indocyanine green retention rate at 15 min; LHL15, liver to liver plus heart uptake ratio at 15 min; AFP, α -fetoprotein; PIVKAI, protein induced by vitamin K absence II; AU, arbitrary units; HAI, Hepatic Activity Index. † χ^2 test, except ‡Mann–Whitney *U* test.

(7.0 per cent). There were no differences in postoperative incidence of pleural effusion, ascites and infections between groups. However, patients with a high PVP significantly more often had liver dysfunction (7 *versus* 2 patients; $P < 0.001$).

Overall and recurrence-free survival

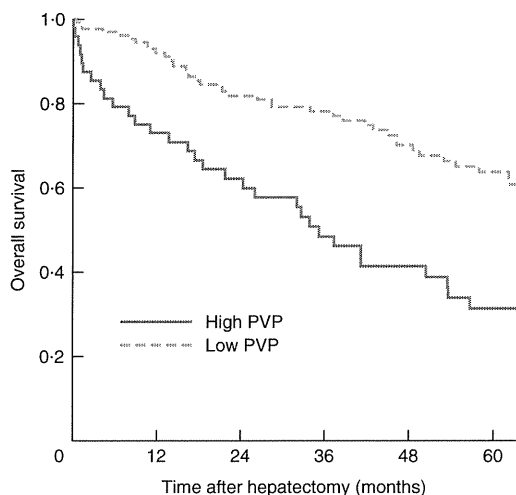
Median follow-up of all patients was 39.2 (range 1.1–207) months. Five patients died from liver failure and sepsis with multiple organ failure after hepatectomy. Recurrence developed after resection in 37 patients (77 per cent) in the high-PVP group and in 93 (72.1 per cent) in the low-PVP group. One-, 3- and 5-year overall survival rates in the low-PVP group were 92.0, 78.2 and 63.7 per cent respectively. This was significantly better than corresponding rates of 73, 49 and 31 per cent in the high-PVP group ($P < 0.001$) (Fig. 1). One-, 3- and 5-year recurrence-free survival rates in the low-PVP group were 73.9, 61.0 and 52.5 per cent

respectively, again better than those in the high-PVP group: 48, 27 and 12 per cent ($P < 0.001$) (Fig. 2).

Prognostic factors for overall and recurrence-free survival

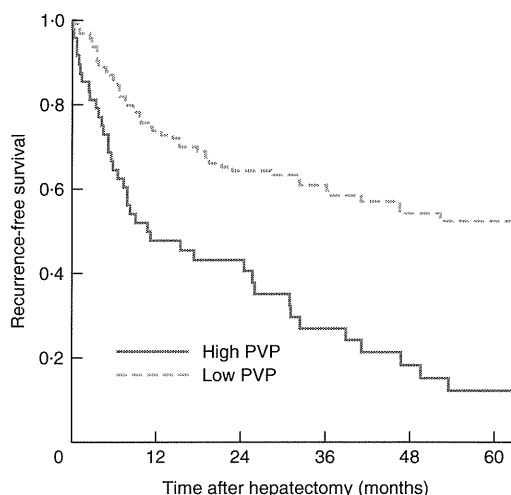
Univariable analysis identified seven significant predictors of poor overall survival: presence of multiple tumours, tumour diameter at least 5 cm, high PVP, liver damage grade B, HAI grade 7 or more, AFP 100 ng/ml or greater and vascular invasion (Table 2). A multivariable analysis based on the significant variables in univariable analysis revealed the presence of multiple tumours, tumour diameter at least 5 cm, high PVP, liver damage and HAI grade 7 or more as independent prognostic indicators for survival.

Table 3 shows the results of univariable analysis to identify factors related to recurrence. Poor prognostic factors were the presence of multiple tumours, tumour diameter



| No. at risk | 0 | 12 | 24 | 36 | 48 | 60 |
|-------------|-----|-----|----|----|----|----|
| High PVP | 48 | 35 | 28 | 21 | 17 | 12 |
| Low PVP | 129 | 112 | 93 | 74 | 58 | 46 |

Fig. 1 Comparison of overall survival of patients with hepatocellular carcinoma and high or low portal venous pressure (PVP) after hepatectomy. $P < 0.001$ (log rank test)



| No. at risk | 0 | 12 | 24 | 36 | 48 | 60 |
|-------------|-----|----|----|----|----|----|
| High PVP | 48 | 22 | 16 | 10 | 6 | 4 |
| Low PVP | 129 | 79 | 66 | 49 | 36 | 27 |

Fig. 2 Comparison of recurrence-free survival of patients with hepatocellular carcinoma and high or low portal venous pressure (PVP) after hepatectomy. $P < 0.001$ (log rank test)

at least 5 cm, HAI grade 7 or more, high PVP, vascular invasion and AFP level 100 ng/ml or greater. The presence of multiple tumours, tumour diameter at least 5 cm and an HAI grade 7 or greater were identified as significant independent prognostic indicators for recurrence in the multivariable analysis.

Discussion

Portal hypertension is considered to be a contraindication to liver resection according to the guidelines of the European Association for the Study of the Liver/American Association for the Study of Liver Diseases^{5,6}. These guidelines indicate that treatment of HCC for such patients

Table 2 Results of univariable and multivariable Cox proportional hazards analyses of prognostic factors for overall survival after hepatectomy

| | Univariable analysis | | Multivariable analysis | |
|--|----------------------|---------|------------------------|---------|
| | Hazard ratio | P | Hazard ratio | P |
| ≥ 2 tumours | 3.15 (2.02, 4.90) | < 0.001 | 2.52 (1.58, 4.02) | < 0.001 |
| Tumour diameter ≥ 5 cm | 1.67 (1.09, 2.54) | 0.018 | 2.22 (1.41, 3.50) | 0.001 |
| PVP ≥ 20 cmH ₂ O | 2.44 (1.60, 3.60) | < 0.001 | 1.74 (1.24, 3.03) | 0.004 |
| Liver damage grade B | 1.91 (1.19, 3.07) | 0.007 | 1.74 (1.07, 2.82) | 0.026 |
| HAI grade ≥ 7 | 2.14 (1.42, 3.25) | < 0.001 | 1.65 (1.04, 2.63) | 0.034 |
| AFP ≥ 100 ng/ml | 1.69 (1.11, 2.57) | 0.013 | 1.24 (0.80, 1.93) | 0.354 |
| Vascular invasion | 1.68 (1.08, 2.61) | 0.020 | 1.21 (0.71, 2.03) | 0.521 |
| Platelet count ≤ 10 × 10 ⁴ /mm ³ | 0.99 (0.60, 1.63) | 0.985 | | |
| ICG-R15 ≥ 15% | 1.21 (0.81, 1.80) | 0.354 | | |
| LHL15 ≤ 0.9 | 0.60 (0.34, 1.07) | 0.079 | | |
| PIVKaII ≥ 100 mAU/ml | 0.85 (0.53, 1.37) | 0.515 | | |
| Child–Pugh grade B | 1.49 (0.83, 2.70) | 0.177 | | |
| Partial hepatectomy | 1.17 (0.77, 1.76) | 0.465 | | |
| HAI stage 4 | 1.31 (0.84, 2.03) | 0.237 | | |

Values in parentheses are 95 per cent confidence intervals. PVP, portal venous pressure; HAI, Hepatic Activity Index; AFP, α-fetoprotein; ICG-R15, indocyanine green retention rate at 15 min; LHL15, liver to liver plus heart uptake ratio at 15 min; PIVKAI, protein induced by vitamin K absence II; AU, arbitrary units.

Table 3 Results of univariable and multivariable Cox proportional hazards analyses of prognostic factors for recurrence after hepatectomy

| | Univariable analysis | | Multivariable analysis | |
|--|----------------------|---------|------------------------|---------|
| | Hazard ratio | P | Hazard ratio | P |
| ≥ 2 tumours | 2.49 (1.68, 3.69) | < 0.001 | 2.30 (1.49, 3.54) | < 0.001 |
| Tumour diameter ≥ 5 cm | 1.86 (1.27, 2.72) | 0.001 | 2.19 (1.39, 3.17) | < 0.001 |
| HAI grade ≥ 7 | 1.77 (1.21, 2.57) | 0.003 | 1.72 (1.16, 2.56) | 0.007 |
| PVP ≥ 20 cmH ₂ O | 1.65 (1.10, 2.48) | 0.014 | 1.29 (0.82, 2.06) | 0.328 |
| Vascular invasion | 1.65 (1.10, 2.48) | 0.015 | 1.22 (0.76, 1.99) | 0.479 |
| AFP ≥ 100 ng/ml | 1.49 (1.01, 2.23) | 0.047 | 1.34 (0.88, 2.04) | 0.189 |
| Platelet count ≤ 10 × 10 ⁴ /mm ³ | 1.04 (0.66, 1.65) | 0.854 | | |
| ICG-R15 ≥ 15% | 1.30 (0.94, 1.96) | 0.160 | | |
| LHL15 ≤ 0.9 | 0.74 (0.48, 1.17) | 0.195 | | |
| PIVKaII ≥ 100 mAU/ml | 1.39 (0.95, 2.03) | 0.085 | | |
| Child–Pugh grade B | 1.09 (0.60, 1.98) | 0.775 | | |
| Liver damage grade B | 1.36 (0.87, 2.13) | 0.167 | | |
| Partial hepatectomy | 1.08 (0.74, 1.57) | 0.704 | | |
| HAI stage 4 | 1.01 (0.66, 1.55) | 0.957 | | |

Values in parentheses are 95 per cent confidence intervals. HAI, Hepatic Activity Index; PVP, portal venous pressure; AFP, α -fetoprotein; ICG-R15, indocyanine green retention rate at 15 min; LHL15, liver to liver plus heart uptake ratio at 15 min; PIVKAIL, protein induced by vitamin K absence II; AU, arbitrary units.

should be local therapy, such as radiofrequency ablation or transarterial chemoembolization. However, in recent years liver resection has been performed safely in patients with cirrhosis.

Bruix and colleagues⁷ reported that a hepatic venous pressure gradient (HVPG) of at least 10 mmHg was the most powerful predictor of postoperative liver failure in patients with cirrhosis⁷. Capussotti and co-workers¹⁴ observed that survival was worse in patients with portal hypertension than in those without, although among patients with Child–Pugh grade A disease the results were similar for those with or without portal hypertension. On the other hand, Imamura and co-workers³ analysed 1056 consecutive liver resections (532 for HCC, 262 for other liver malignancies, 57 for biliary tract malignancy, 174 living donor and 31 for other disease) that did not result in death over a period of 8 years. They concluded that portal hypertension and liver cirrhosis did not affect overall postoperative complications in patients with HCC, and identified blood loss greater than or equal to 1000 ml as the major risk factor. Cucchetti *et al.*¹⁵ performed a retrospective one-to-one matched analysis of 241 patients with cirrhosis divided in two groups according to the presence or absence of portal hypertension. They identified preoperative Model of End-Stage Liver Disease score as the major determinant of postoperative outcome; portal hypertension in this analysis did not affect postoperative complication rates in patients with HCC.

In the present study high PVP was related to liver inflammation and fibrosis, as evidenced by the lower platelet count, prothrombin time and albumin level, and

higher Child–Pugh grade, HAI grade and stage. Partial hepatectomies or segmentectomies, that is limited hepatic resections of the liver, were deemed appropriate more often for patients with a high PVP as patients with a PVP of 20 cmH₂O or greater are more likely to develop hyperbilirubinaemia after hepatectomy¹⁰. Limited resections for patients with liver cirrhosis proved to be an effective treatment for HCC to avoid liver dysfunction and death after hepatectomy in the authors' unit¹⁶.

HCC can arise anywhere in severely cirrhotic liver as multicentric carcinogenesis. Minute and 'undetectable' HCC may be found in explanted livers of patients with severe cirrhosis at liver transplantation¹⁷. The differences between the present data and those of other reports may have resulted from varying cut-off values of PVP. The Barcelona Clinic Liver Cancer group considered patients to have portal hypertension based on the presence of oesophageal varices, splenomegaly and a platelet count below 100 000/mm³. This differs markedly from the direct measurement of portal vein pressure during surgery⁷. Figueras and colleagues¹⁸ reported that PVP at the beginning of surgery, HVPG, high central venous pressure (CVP) and intraoperative blood loss were factors associated with complications after liver resection. In the present authors' institution, CVP before liver resection was usually 5 mmHg, and it was assumed that a PVP of 20 cmH₂O before liver resection would be equivalent to a PVP of 15 mmHg and an HVPG of 10 mmHg (HVPG = PVP – CVP). However, detailed data concerning the CVP at the start of surgery were not available in this study.

Capussotti and co-workers¹⁴ showed that the presence of portal hypertension in patients with Child–Pugh grade A disease did not affect overall survival. Ripoll⁸ reported that portal hypertension, assessed via HPV, was an independent predictor of survival. The present data support these results; overall and recurrence-free survival rates after hepatectomy were worse in patients with high PVP (at least 20 cmH₂O) assessed by direct measurement. In this study, overall survival was lower in patients with high PVP because of their worse liver function. A high PVP may have reflected inflammation and fibrosis in the liver, and been associated with liver dysfunction, because HAI grade of the background liver and stage were worse in the high-PVP group than in the low-PVP group. Multivariable analysis of predictors of recurrence revealed that the presence of multiple and large tumours, and inflammation in the remnant liver, were associated with earlier recurrence of HCC after hepatectomy even after curative resection. Indeed, high PVP was not associated with recurrence, although recurrence-free survival in high-PVP group was significantly worse than in the low-PVP group.

In contrast to intraoperative portal pressure measurement, HPV measurement allows selection of patients before surgery and so this may ultimately be more appropriate in the future.

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References

- 1 Yang JD, Robert LR. Hepatocellular carcinoma: a global view. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 448–458.
- 2 Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK *et al.* Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. *Ann Surg* 2004; **240**: 698–708.
- 3 Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K *et al.* One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg* 2003; **138**: 1198–1206.
- 4 Teh SH, Christein J, Donohue J, Que F, Kendrick M, Farnell M *et al.* Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: Model of End-Stage Liver Disease (MELD) score predicts perioperative mortality. *J Gastrointest Surg* 2005; **9**: 1207–1215.
- 5 Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005; **42**: 1208–1236.
- 6 Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK *et al.*; EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421–430.
- 7 Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC *et al.* Surgical resection of hepatocellular carcinoma in cirrhotic patients; prognostic value of preoperative portal pressure. *Gastroenterology* 1996; **111**: 1018–1022.
- 8 Ripoll C. Hepatic venous pressure gradient and outcomes in cirrhosis. *J Clin Gastroenterol* 2007; **41**(Suppl 3): S330–S335.
- 9 Kanematsu T, Furui J, Yanaga K, Okudaira S, Kamohara Y, Eguchi S. Measurement of portal venous pressure is useful for selecting the optimal type of resection in cirrhotic patients with hepatocellular carcinoma. *Hepatogastroenterology* 2005; **52**: 1828–1831.
- 10 Kanematsu T, Takenaka K, Furuta T, Ezaki T, Sugimachi K, Inokuchi K. Acute portal hypertension associated with liver resection. Analysis of early postoperative death. *Arch Surg* 1985; **120**: 1303–1305.
- 11 The Liver Cancer Study Group of Japan. *The General Rules for the Clinical and Pathological Study of Primary Liver Cancer* (3rd edn). Kanehara: Tokyo, 2010.
- 12 Ogura Y, Hori T, El Moghazy WM, Yoshizawa A, Oike F, Mori A *et al.* Portal pressure < 15 mm Hg is a key for successful adult living donor liver transplantation utilizing smaller grafts than before. *Liver Transpl* 2010; **16**: 718–728.
- 13 Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F *et al.* Histological grading and staging of chronic hepatitis. *J Hepatol* 1995; **22**: 696–699.
- 14 Capussotti L, Ferrero A, Viganò L, Muratore A, Polastri R, Bouzari H. Portal hypertension: contraindication to liver surgery? *World J Surg* 2006; **30**: 992–999.
- 15 Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, Ramacciato G *et al.* Is portal hypertension a contraindication to hepatic resection? *Ann Surg* 2009; **250**: 922–928.
- 16 Kanematsu T, Takenaka K, Matsumata T, Furuta T, Sugimachi K, Inokuchi K. Limited hepatic resection effective for selected cirrhotic patients with primary liver cancer. *Ann Surg* 1984; **199**: 51–56.
- 17 Hidaka M, Eguchi S, Okudaira S, Takatsuki M, Tokai H, Soyama A *et al.* Multicentric occurrence and spread of hepatocellular carcinoma in whole explanted end-stage liver. *Hepatol Res* 2009; **39**: 143–148.
- 18 Figueras J, Llado L, Ruiz D, Ramos E, Busquets J, Rafecas A *et al.* Complete *versus* selective portal triad clamping for minor liver resections: a prospective randomized trial. *Ann Surg* 2005; **241**: 582–590.

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- B** Data Collection
- C** Statistical Analysis
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- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

The usefulness of a high-speed 3D-image analysis system in pediatric living donor liver transplantation

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Summary

Background:

Since March 2010, we have used a high-speed 3D-image analysis system (SYNAPSE VINCENT) to calculate the graft volume in living donor liver transplantation (LDLT) to replace CT volumetry. The SYNAPSE VINCENT is capable of extracting each vessel territory in the liver and displaying 3D images simply, quickly, and accurately. Therefore, we report here the usefulness of the SYNAPSE VINCENT in pediatric LDLTs in overcoming issues with perfusion area of hepatic venous tributaries in monosegmental grafts.

Material/Methods:

The SYNAPSE VINCENT was used in three pediatric patients. In two of these cases, the possibility of monosegmental grafts was assessed when calculating graft volumetry of segment III.

Results:

The graft recipient weight ratio (GRWR) with graft volumetry measurements of the left lateral segment were 1.8–5.6%. GRWR of segment III were 2.3 and 2.0%. Since donor V2, venous branch to segment II and V3, venous branch to segment III were independently branching in one case, the monosegmental graft could be evaluated preoperatively according to the venous perfusion.

Conclusions:

Graft volumetry using the SYNAPSE VINCENT was useful for planning the LDLT operative procedures, especially in infants possibly in need of monosegmental graft.

Key words:

high-speed 3D-image analysis system • graft volumetry • living related liver transplantation • hepatic venous perfusion area • children

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BACKGROUND

CT volumetry is used to calculate graft volume in living donor liver transplantation (LDLT). Traditional volumetry involves freehand tracing, which takes time and effort. Additionally, there is inevitable variation in the results from each analyst, and detailed analysis (i.e., individual vessel territory) is difficult [1].

In this study, we used a high-speed 3D-image analysis system (SYNAPSE VINCENT; Fuji Photo Film Co., Ltd.) to calculate graft volume in LDLTs. This system is capable of extracting each vessel territory in the liver using contrast-enhanced CT images and displaying 3D images simply (using a single click), quickly (within a few minutes), and accurately (Figure 1A, B).

LDLT, particularly in infants, is often limited by larger grafts, even when using a left-lateral segment graft. Therefore, monosegmental grafts, or reduced grafts, may have to be introduced [2]. In monosegmental grafts, the perfusion area of hepatic venous tributaries poses a problem. In order to overcome this problem, the usefulness of the SYNAPSE VINCENT in pediatric LDLT was investigated.

MATERIAL AND METHODS

Since March 2010, the SYNAPSE VINCENT was used to calculate graft volume in LDLT for three pediatric patients with biliary atresia at our department of Nagasaki University Hospital (Table 1). Case 1 was a 10-month-old male (height/weight at LDLT: 66 cm/6.7 kg) whose donor was his father (height/weight at LDLT: 167 cm/63 kg); case 2 was a 6-month-old female (61.2 cm/6.4 kg) whose donor was her mother (156 cm/57.2 kg); case 3 was a 7-year-old male (124.5 cm/23.8 kg) whose donor was his father (166 cm/58 kg). In two of the three cases, the possibility of monosegmental grafts was assessed and taken into consideration when calculating the graft volumetry of segment III.

RESULTS

Preoperative graft volumetry measurements of the left lateral segment were 377 ml (5.6% in the graft recipient weight ratio; GRWR), 278 ml (4.3%), and 427 ml (1.8%) for cases 1, 2, and 3, respectively. The graft volumetry measurements of segment 3 were 157 ml (2.3% in the GRWR) and 129.4 ml (2.0%) for cases 1 and 2,

respectively (Table 2). In case 2, it was feasible to extract each segmental hepatic venous perfusion area using the SYNAPSE VINCENT. In this case, since donor's V2, venous branch to segment II and V3, venous branch to segment III showed independent branching, the monosegmental graft could be more accurately evaluated according to the venous perfusion using the graft volumetry of segment III preoperatively (Figure 2).

The actual graft weights were 324 g (4.8% in the GRWR), 281 g (4.4%), and 407 g (1.7%) for cases 1, 2, and 3, respectively (Table 2). There were almost no differences between expected preoperative graft volumetry and actual graft weights. The recipient liver weights were 257 g, 340 g, and 668 g for cases 1, 2, and 3, respectively. The lateral segments were used in all three cases with primary closure of the abdominal wall. Intraoperative and postoperative courses were uneventful in all cases; neither vascular nor bile duct complications were detected.

DISCUSSION

Liver transplantation (LT) is an established curative therapy for children with end-stage chronic liver disease or acute liver failure. Outcomes following LT in children have significantly improved over the past two decades, due to advances in surgical procedures, organ preservation technology, immunosuppressive management, and perioperative care. A shortage of full-sized grafts from pediatric donors once produced high waiting-list mortality in the pediatric population, especially in children younger than 5 years old, and prompted the identification of alternative graft sources for pediatric patients. To increase the supply of appropriately-sized organs for pediatric recipients, the techniques of reduced graft, split graft, and LDLT were developed, which thus expanded the potential donor pool and led to a significant decrease in waiting-list mortality for children [3].

LDLT, especially in infants, is often limited by graft size, even when using a left-lateral segment graft [2]. An over-sized transplanted graft causes two major complications. First, inadequate perfusion of the liver results in graft dysfunction, and second, abdominal wall closure can cause graft compression or diaphragmatic splinting, resulting in respiratory complications [4]. As a result, monosegmental or reduced grafts were introduced particularly in cases of infant LDLT [2]. The initial indication for monosegmental LT was