used with careful perioperative management [15]. Furthermore, we reported that a left-lobe graft, usually a "small-for-size" graft, is an important option in LDALT, judging from the standpoint based on both donor safety and benefit of the recipient [16]. Therefore, it is recommended that left-lobe grafts be used.

LDALT is considered to be one of the procedures still on a learning curve. Both the minimum graft volume and the risk factors closely related to graft survival in LDALT remain unclear, therefore, it is extremely important to assess these problems. The aim of this study is to clarify whether graft size is a critical risk factor for graft survival in LDALT.

Patients and methods

Patient cohort

We included 73 LDALTs, except for auxiliary transplantation and blood-type incompatible cases, from May 1997 to July 2002 in this study. The patient group consisted of 31 men and 42 women, ranging in age from 18 to 70 years. The indication for LDALT consisted of fulminant hepatic failure in 24 cases, primary biliary cirrhosis in 16, viral liver cirrhosis including hepatocellular carcinoma in 24, primary sclerosing cholangitis in 2, familial amyloid polyneuropathy in 2, and other reasons in 5. There were 58 left-lobe grafts and 15 right-lobe grafts. All left-lobe grafts were extended left-lobe grafts including the middle hepatic vein; 44 of the 58 left-lobe grafts included the left caudate lobe.

All patients had a monthly follow up, and the median follow-up period was 358 days with 94 days and 1019 days as a 25th percentile and 75th percentile respectively. Graft survival was defined as the time period between LDALT and graft loss, either by patient death or by graft failure necessitating a retransplant.

Evaluation and selection of graft

Evaluation and selection criteria for a liver graft were described previously [15, 16]. Briefly, the standard liver volume was calculated according to the formula developed by Urata et al. [17]. Liver volume was estimated by preoperative computed abdominal tomography (CT) scanning, and in principle, GV divided by SLV over 30% is the ideal requirement. Our policy requires that a left-lobe graft is selected first and that the volume of the left-lobe graft is clearly less than 30% of SLV and approximately 25% of SLV, if this is not the case a right-lobe graft or auxiliary partial graft is chosen. Preoperative assessment of a three-dimensional CT was routinely performed, to ensure the parenchymal division line and the number and size of draining veins [18].

Surgical technique and postoperative care

The graft harvesting technique, recipient operation and perioperative patient management of recipients, including immunosuppression regimen, are described elsewhere [15, 16]. Briefly, the right-lobe grafts were excised using an ultrasonic dissector and electrocautery at the right side of Cantlie's line, which meant no middle hepatic vein was included in any of the right-lobe grafts. All branches from the middle hepatic vein were divided between the silk ties, except in one case. In all left-lobe grafts, the right first Glisson's branch including portal vein and hepatic artery were clamped; a demarcated line was observed on the right side of Cantlie's line. Parenchymal division was performed along a line 5 mm right of the demarcated line, therefore, all left-lobe grafts included a middle hepatic vein and a part of the anterior segment, which was perfused from left side vascular vessels. During the parenchymal division inside the liver, the cutting plane was made near the anterior Glisson's branch and right hepatic vein.

Grouping

The patients were divided into two groups, according to graft volume and standard liver volume: group 1 (small-size group; GV/SLV $<40\%$), and group 2 (non-small-size group; GV/SLV $\geq 40\%$). Perioperative clinical data were compared between the two groups, including graft survival and postoperative complications. These parameters were also compared for the conditions of cirrhotic recipients. Urgent status due to chronic liver disease was defined as patient's status requiring critical care in hospital due to chronic liver, including plasma exchange and continuous hemodiafiltration.

Statistics

The data were expressed as medians (25th percentile and 75th percentile). Comparisons of continuous variables were made using the Mann-Whitney U test. The chi-square test was used to compare the qualitative data. Graft survival was calculated by the product limit method of Kaplan and Meier, and the differences in the survival between the groups were then compared using the log-rank test. The software of StatView (Version 4.11; Abacus Concepts, Berkeley, CA94704–1014, USA) was used for all analyses on a Macintosh computer. A P value of less than 0.05 was considered statistically significant.

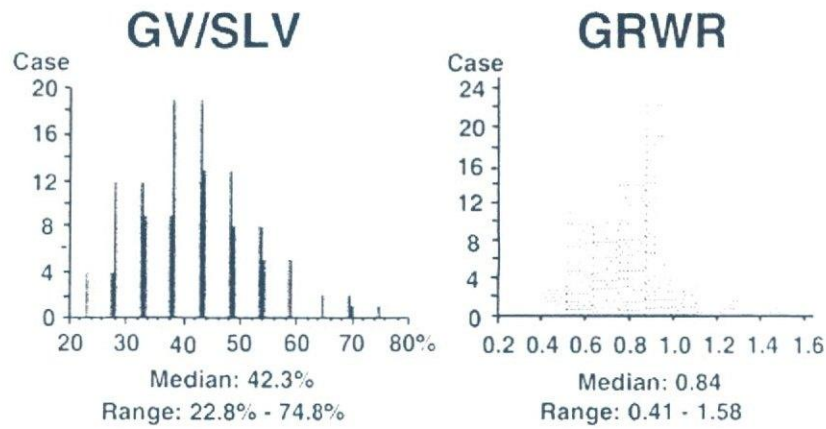

Fig. 1 Distribution of cases according to graft size; most grafts were "small-for-size" grafts

Results

There was no mortality of donors; postoperative complications which prolonged donor's hospital stay were: bile duct stenosis in two cases, abdominal abscess by meticilline-resistant *Staphylococcus aureus* in one, and bile leakage in one. Median postoperative hospital stay of the donors was 11.5 days, ranging from 5 days to 43 days. Graft size as GV/SLV ranged from 22.8% to 74.8%, with a median of 42.3%, and graft recipient weight ratio (GRWR) ranged from 0.41 to 1.58, with a median of 0.84 (Fig. 1).

A comparison of perioperative clinical variables among the two groups is shown (Table 1). Patients in group 1 were younger than those in group 2. Postoperative peak levels of aspartate aminotransferase, alanine aminotransferase and bilirubin in group 1 were lower than in group 2. Postoperative hospital stay in group 1 was shorter than in group 2. Examination of the graft's variables showed that the proportion of left-lobe grafts in group 1 was higher than in group 2. Graft weight, GV/SLV, and graft-recipient weight ratio in group 1 were lower than in group 2. Recipient variables showed no differences, except for gender, which was found in preoperative variables, including the Child–Pugh's class C, urgent status due to chronic liver disease, hyperbilirubinemia, and ascites. Operative time and blood loss in group 1 tended to be lower than in group 2. The incidence of postoperative hyperbilirubinemia (over 10 mg/dl at postoperative day 14) in group 1 was lower than in group 2. No difference was found in other variables, including postoperative intractable ascites, postoperative complications and incidence of acute cellular rejection.

The risk factors closely related to graft survival were: a preoperative urgency status, urgent status due to chronic liver disease, and ABO blood-type compatibility (not identical but compatible combination). A preoperative bilirubin value over 10 mg/dl and Child–Pugh's class C tended to be related to poor graft survival. In contrast, graft kind (left-lobe graft or right-lobe graft) and graft size were not always significant risk factors (Table 2).

When comparing graft survival curves, no significant difference was observed between group 1 and group 2 (Fig. 2). When graft survival curves in cirrhotic recipients, who were classified into the Child–Pugh's class C, are compared, no definite difference was found between group 1 and group 2 (Fig. 3).

Discussion

The distribution of graft size in this study ranged from 22.8 to 74.8% as GV/SLV with a median of 42.3%, and GRWR ranged from 0.41 to 1.58% with a median of 0.84% (Fig. 1). Most grafts in this study were surprisingly "small-for-size". In terms of donor selection criteria, the left-lobe graft is, in principle, selected for use when the donor's graft volume, using an extended left lobe plus caudate lobe, is more than 30% of standard liver volume. If the graft volume is clearly less than 30% of standard liver volume (approx. 25%) a right-lobe graft or an auxiliary partial graft is then selected. The minimum liver volume, needed to meet metabolic demand, was reported to be less than 20% of the liver in non-cirrhotic patients [19]. In LDALT, a liver graft with 25% of the standard liver volume was reported to be successful for fulminant hepatic failure [6]. In this study, a patient with fulminant hepatic failure, whose liver graft was 22.8% of his standard liver volume, quickly recovered and obtained good initial function, although he unfortunately died of chronic rejection on postoperative day 205. However, in general, the graft size is known to critically influence the outcome of LDALT. Tanaka et al. [3] reported that the use of "small-for-size grafts" (< 1% of graft-recipient weight ratio) leads to lower graft survival. Miller et al. [2] reported that graft function and survival were influenced not only by graft

Table 1 Comparison between clinical variables of group 1 and group 2. (*Group 1* small group in which graft volume was <40% of standard liver volume, *group 2* non-small group, in which graft volume was ≥40% of standard liver volume, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *FHF* fulminant hepatic failure, *PBC* primary biliary cirrhosis, *LC* viral cirrhosis, including hepatocellular carcinoma, *PSC* primary sclerosing cholangitis, *FAP* familial amyloid polyneuropathy, *HAT* hepatic artery thrombosis, *PVT* portal vein thrombosis, CMV cytomegalovirus)

Variables	Group 1 ($n=26$)	Group 2 ($n=47$)	P value
Donor variables			
Age (years)	29 (23, 35)	44 (28, 50)	<0.01
Gender (male/female)	15/11	33/14	0.31
Blood loss (ml)	788 (470, 1000)	700 (364, 1200)	0.58
Operating time (min)	429 (355, 506)	448 (405, 483)	0.65
Postoperative AST (IU/l)	236 (202, 353)	336 (239, 469)	<0.05
Postoperative ALT (IU/l)	266 (180, 368)	361 (233, 460)	<0.05
Postoperative bilirubin (mg/dl)	1.5 (1.3, 1.9)	2.1 (1.6, 3.5)	<0.01
Postoperative hospital stay (days)	11 (9, 14)	14 (10, 167)	<0.01
Graft variables			
Graft kind	–	–	<0.05
Right lobe	0	15	–
Left lobe	7	7	–
Left lobe and caudate lobe	19	25	–
ABO compatibility	–	–	0.55
Identical	22	36	–
Compatible	4	11	–
Graft weight (g)	368 (330, 410)	520 (463, 588)	<0.01
GV/SLV (%)	32.1 (28.9, 35.7)	45.9 (42.5, 50.5)	<0.01
GRWR	0.61 (0.56, 0.69)	0.90 (0.83, 0.98)	<0.01
Recipient variables			
Age(years)	48 (39, 57)	48 (42, 54)	0.95
Gender (male/female)	15/11	16/31	0.08
Diagnosis			
FHF	10	14	–
PBC	5	11	–
LC	8	16	–
PSC	1	1	–
FAP	0	2	–
Others	2	3	–
Preoperative bilirubin (mg/dl)	8.3 (3.2, 17.0)	11.3 (3.6, 17.9)	0.46
Preoperative bilirubin >10 mg/dl	12 (46.2%)	27 (57.4%)	0.51
Preoperative ascites	10 (38.5%)	21 (44.7%)	0.63
Child–Pugh class			
A	3	5	–
B	2	2	–
C	11	29	–
FHF	10	11	–
Esophageal varices	10 (38.5%)	23 (48.9%)	0.46
Urgent status due to chronic liver disease[a]	2 (7.7%)	8 (17.2%)	0.48
Operating time (min)	717 (621, 838)	797 (716, 926)	0.05
Blood loss (ml)	4510 (2600, 7300)	6040 (4000, 10032)	0.1
Postoperative persistent cholestasis	3 (11.5%)	19 (40.4%)	0.02
Postoperative intractable ascites (>1 l/day at postoperative day 14)	4 (15.4%)	4 (8.5%)	0.44
Postoperative complications			
Biliary			
Leakage	2	5	–
Stenosis	2	0	–
Bleeding	1	0	–
Vascular			–
HAT	2	1	–
PVT	1	0	–
Infarction	1	2	–
Infection			–
Sepsis	1	1	–
CMV-related	0	2	–
Fungus-related	1	1	–
Others	4	8	–
Acute cellular rejection	6 (23.1%)	16 (34.0%)	–

[a]Defined as patient's status requiring critical care in hospital due to chronic liver, including plasma exchange and continuous hemodiafiltration

size, but also by pre-transplantation disease severity. A graft-recipient weight ratio as low as 0.6% can be used safely in patients without cirrhosis or in patients with Child–Pugh's class A. Transplant recipients with Child–Pugh's class B or C require a graft-recipient weight ratio greater than 0.85% to avoid "small-for-size" syndrome

Table 2 Risk factors related to graft survival

Variables		1-Year survival	*P* value
ABO compatibility	Identical ($n=58$)	86.20%	0.01
	Compatible ($n=15$)	58.20%	–
Preoperative bilirubin >10 mg/dl	Present ($n=39$)	69.50%	0.08
	Absent ($n=34$)	93.10%	–
Child–Pugh class C[a]	Present ($n=39$)	79.40%	0.22
	Absent ($n=12$)	90.90%	–
Urgent status due to chronic liver disease[b]	Present ($n=10$)	51.40%	0.009
	Absent ($n=63$)	84.10%	–
Graft kind	Left lobe ($n=58$)	79.00%	0.47
	Right lobe ($n=15$)	84.60%	–
Graft size	Extra-small ($n=7$)	85.70%	0.4
	Small ($n=19$)	65.00%	–
	Medium ($n=34$)	83.50%	–
	Medium-large ($n=13$)	90.90%	–

[a]Fulminant hepatic failure was excluded
[b]Defined as patient's status requiring critical care in hospital due to chronic liver, including plasma exchange and continuous hemodiafiltration

and related complications. Makuuchi et al. [4] also recommended that a larger graft is necessary for high-risk patients with primary biliary cirrhosis (updated Mayo risk scores of more than 12). In contrast, in this study it is of great interest that no significant difference in graft survival rates was found between the two groups, not only in all patients but also in a subgroup of cirrhotic patients with Child–Pugh's class C in which the influence of a "small-for-size" graft is enhanced on outcome of LDALT. When assessing the reasons why graft survival rate of the Child–Pugh's class C patients in group 2 (with a larger graft) tended to be poorer than in group 1 (with smaller graft), one possible reason is that the incidence of urgent status due to chronic liver disease in group 2 (27.6%) tended to be higher than that in group 1 (18.2%). Another possible reason was the incidence of liver cancer in group 2 (31.0%) which tended to be higher than in group 1 (18.2%), furthermore, two patients in group 2 died of cancer recurrence (6 months and 24 months after operation, respectively). Graft-survival analysis was carried out using two subgroups: patients with acute liver failure and those with chronic liver insufficiency (data not shown). In the subgroup of patients with acute liver failure, the graft survival in group 1 (with smaller graft) tended to be better than that in group 2 (with larger graft). In contrast, the graft survival in group 1 was similar to that in group 2 in the subgroup of patients with chronic liver insufficiency (especially Child–Pugh's class C patients) (Fig. 3).

From an ethical point of view, donor safety has priority. Unfortunately, in LDALT, the need of larger-size grafts for children has encouraged the use of right hepatic lobes from living donors. As a result, mortality of right-lobe donors was reported to be nearly 1% in western countries [11]. In Japan, however, donor mortality was not reported until July 2002 (in more than 2,000 LDLTs). We previously reported that postoperative peak values of aspartate aminotransferase and total bilirubin in right-lobe donors were higher than in left-lobe donors. Furthermore, postoperative hospital stay in right-lobe donors was longer than in left-lobe donors. These facts clearly indicate that potential risks in right-

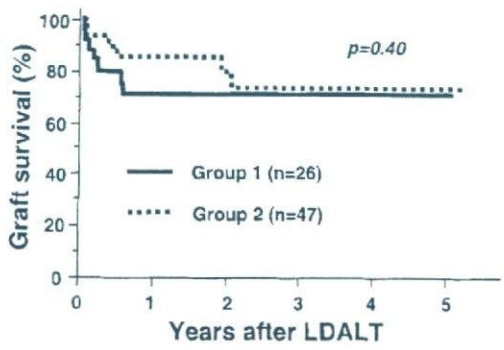

Fig. 2 Graft survival according to graft size. No significant difference in graft survival was found among the four groups. *Group 1* small-size group, in which graft volume was <40% of standard liver volume, *group 2* non-small-size group, in which graft volume was ≥40% of standard liver volume

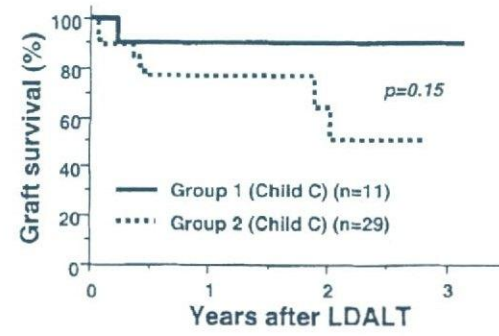

Fig. 3 Graft survival according to graft size in patients with Child–Pugh's class C liver cirrhosis. No difference in graft survival was found among the four groups. *Group 1* small-size group, in which graft volume was <40% of standard liver volume, *group 2* non-small-size group, in which graft volume was ≥40% of standard liver volume

lobe donors were higher than in left-lobe donors; the same results were obtained in this study. To minimize potential risks for living donors, left-lobe grafts for adult recipients (small-for-size grafts), should be carefully reassessed. Factors related to graft failure of "small-for-size" grafts are considered to be: (1) graft injury due to excessive portal flow and/or portal pressure, and (2) excessive metabolic and synthetic demand of recipients. Portal venous decompression was reported to improve survival of canine partial liver transplantation [20]. The effect of a porto-hepatic vein shunt on portal vein decompression might be an important factor for preventing graft injury after recirculation in an extremely small graft. In France, a new technique for adult liver transplantation using a "small-for-size" graft was reported in order to avoid graft congestion and failure by over perfusion, in which the superior mesenteric venous flow was diverted by a mesocaval shunt with downstream ligation of the superior mesenteric vein [21]. Splenectomy of splenic artery ligation might be another alternative to obtain a better outcome in LDALT using "small-for-size" grafts. Splenectomy was reported to generate the following merits: reduction of graft congestion leading to improvement of the hepatic renal functions; improvement of thrombocytopenia persistence after liver transplantation; avoidance of bleeding episodes related to left-sided portal hypertension [22]. Makuuchi et al. [23] also reported that splenectomy in LDLT is an acceptable treatment option in patients with thrombocytopenia or when hepatopetal portal flow must be obtained by closure of splenorenal shunt. However, further investigations are necessary to make definite conclusions.

The following were risk factors closely related to poor graft survival: poor prognostic factors for graft survival; the urgent status due to chronic liver disease; preoperative bilirubin value of more than 10 mg/dl; ABO blood-type compatibility. Urgency status is also known to be one of the risk factors associated with graft loss in cadaveric liver transplantation using whole-liver grafts [24]. Therefore, another therapeutic strategy rather than procurement of a larger-size graft would be necessary for high-risk patients.

Humar [25] recently commented on graft selection, with citation of our previous article (Arch Surg 2002), that transplant teams should not limit themselves to either the left-lobe or right-lobe graft. Rather, the recipient's size should be factored together with the severity of the recipient's liver disease on the best liver graft for that particular recipient with minimal risk to the donor. For smaller recipients or those with model for end-stage liver disease score, a left lobe may be the best choice. For others, especially those with more advanced liver disease, a right lobe could be the best option. This opinion sounds reasonable.

In conclusion, the graft survival rates according to graft size were not different, furthermore, the graft survival rates in patients with Child–Pugh's class C liver cirrhosis were similar. The risk factors affecting the graft survival were preoperative hyperbilirubinemia, compatible but not identical ABO blood type combination between donor and recipient, and the urgent status due to chronic liver disease. The graft size was not always considered to be a critical risk factor for LDALT, therefore, a left-lobe graft, even a "small-for-size" graft, remains a feasible option in LDALT.

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TRANSPLANTATION

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A SIMPLE AND ACCURATE FORMULA TO ESTIMATE LEFT HEPATIC GRAFT VOLUME IN LIVING-DONOR ADULT LIVER TRANSPLANTATION

NOBORU HARADA, MITSUO SHIMADA, TOMOHARU YOSHIZUMI, TAKETOSHI SUEHIRO, YUJI SOEJIMA, AND YOSHIHIKO MAEHARA

Background. **In the field of living-donor adult liver transplantation, a small-for-size graft often occurs, particularly when using left-lobe grafts. This is because of the limited volumes associated with left-lobe grafts. The accurate preoperative evaluation of graft volumes is crucial to avoid this complication. The aim of this study is to clarify the usefulness of a new formula to estimate the left-lobe graft volume.**

Method. **In 61 left-lobe grafts, a new formula was created with stepwise regression analysis using the following variables: height, weight, the thoracic and abdominal distance from anterior to posterior side (A-P), and distance from left to right side (L-R) of the initial 20 donors. With another 41 donors, the difference between the actual and estimated graft volume using the formula and two-and three-dimensional computed tomography was prospectively evaluated.**

Results. **On the basis of the results of the stepwise regression analysis, a new formula was created as follows: graft volume (ml)=313.4+7.7×weight (kg)−12.6×thoracic L-R (cm). The difference between the actual and estimated graft volumes using the formula was significantly better (10.8±9.5%) than that of the volumetry using two-dimensional computed tomography (16.3±10.1%) ($P<0.05$).**

Conclusions. **In conclusion, the new formula can estimate the actual graft volume more accurately than conventional volumetry with two-dimensional computed tomography. The formula is useful to estimate the volume of left-lobe graft in living-donor adult liver transplantation.**

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Currently, living-donor adult liver transplantation (LDALT) is used to compensate for a serious shortage of cadaveric organs. A small-for-size graft often occurs, particularly when using a left-lobe graft, because partial hepatic grafts are usually smaller than ideal graft volumes for recipients (*1–3*). On the contrary, we have recently reported a favorable outcome for LDALT using left-lobe grafts (*4, 5*).

For successful LDALTs, appropriate evaluation of graft size is one of the most important factors. Two-dimensional computed tomography (2D-CT) or three-dimensional computed tomography (3D-CT) volumetry has been popular and useful for estimating the preoperative graft volumes (*6, 7*); however, there is sometimes a large difference between the actual graft volume and the estimated graft volume using these methods. Although some various formulae (*8, 9*) have been reported to calculate standard liver volumes for recipients using the variables such as height and weight, to our knowledge, no formula in particular has been reported to accurately calculate the volume for left-lobe grafts. Therefore, we analyzed variables including height, weight, thoracic A-P (A-P, distance from anterior to posterior side) diameter, thoracic L-R (L-R, distance from left to right side) diameter, abdominal A-P diameter, and abdominal L-R diameter to develop a new formula that will simply and accurately predict left-lobe liver volume. In this report, we present a new predictive formula to estimate the left-lobe graft volume accurately and compare the usefulness of the formula with that of conventional CT volumetry.

PATIENTS AND METHODS

Donors

From October 1996 to April 2003, a total of 111 LDLTs were performed at Kyushu University Hospital. Among them, 93 donors underwent left lobectomy (including extended left lobectomy), and 18 donors underwent right lobectomy. We studied 61 donors who underwent extended left lobectomy and calculated the hepatic graft volume using 2D- and 3D-CT in LDALT. The indication for 61 LDALTs included primary biliary cirrhosis in 14, hepatitis C cirrhosis in 23, fulminant hepatic failure in 13, retransplantation in 2, Wilson disease in 2, biliary atresia in 1, primary sclerosing cholangitis in 3, and other conditions in 1 patient. The donors were 4 husbands, 4 wives, 10 brothers, 3 sisters, 25 sons, 4 mothers, 2 fathers, 7 daughters, 1 nephew, and an unrelated person in one case.

2D-CT Volumetry

A preoperative evaluation for potential living-related liver donors included a complete history and physical examination and an abdominal CT scan. Preoperative helical CT images were made using 3 mm thick slices represented on a CT machine (X vigor Real, Toshiba, Tokyo, Japan). Enhancement was achieved by an intravenous bolus of contrast medium. This method allows for a clear visualization of the intrahepatic portal veins and the hepatic veins. The 3 mm thick CT slices were scanned using a scanner (Epson GT-9500, Torrance, CA) with a mouse ball device and image handling software (PhotoShop 5.0, Adobe Systems, Mountain View, CA). The entire perimeter of the liver, the left, and the caudate lobe of each slice were outlined, and the enclosed area was simultaneously calculated with image analysis software (NIH image 1.61, Wayne Rasband, National Institutes of Health, Bethesda, MD). The liver volume can then be calculated using the following equation (*6, 8*): V (cm^3)=S×A, where S is the interval of the serial slices (cm), and A is the enclosed area (cm^2).

3D-CT Volumetry

3D reconstructions of the liver and the graft were rendered with the helical CT data using zioM900 (Zio software inc., Tokyo, Japan, http://www.zio.co.jp). The following method was used for the 3D-CT volumetry. The entire 3D image was visualized and reconstructed from 3 mm-slices of helical CT data. By selecting the images of anything except for the liver and by changing the contrast of the CT number, a rough 3D-CT image of the liver can be reconstructed by subtracting those images from the entire image. Images of tissue and vessels surrounding the liver were deleted. When the correct image of the liver was selected, the volume of the liver was measured automatically (*7*).

Surgical Technique

The donor-extended left hepatectomy that included a caudate lobe was performed according to the surgical procedure described elsewhere (*4, 5, 10*) with minor modifications after a thorough preoperative evaluation. In regard to the left-lobe grafts, all left grafts included the middle hepatic vein and a caudate lobe. The actual transection plane for extended left lobectomy with the middle hepatic vein was determined by using intraoperative ultrasonography to refer to the line along the right side of the middle hepatic vein. After a dissection of the left hepatic artery and portal and hepatic veins, extended left-lobe grafts were flushed by way of the portal vein in situ or ex situ and preserved in a cold preservation solution. After a University of Wisconsin solution was used as a flushing and preservation solution, the volume of the graft was measured.

New Formula Estimating Left Hepatic Graft

In the initial 20 LDALTs between May 1999 and October 2000, a new predictive formula was created using stepwise regression analysis with the following variables: height, weight, thoracic A-P and L-R diameter at the level of the processus xiphoideus of the CT image, and abdominal A-P and L-R diameter at the level of the umbilicus of the CT image. Body weight and body height were recorded at the time of the CT examination. The variables such as (1) thoracic A-P diameter (cm), (2) thoracic L-R diameter (cm), (3) abdominal A-P diameter (cm), and(4) abdominal L-R diameter (cm) are shown in Figure 1. $F>4.0$ was considered to be statistically significant.

We prospectively evaluated the accuracy of our new formula using the other 41 grafts completed from November 2000 to April 2003. We evaluated the difference between the actual graft volumes and the other estimated 41 graft volumes, which were calculated using 2D-CT (3 mm slice). We also evaluated the difference between the actual graft volumes and the other estimated 41 graft volumes that were calculated using 3D-CT.

Measurement of Actual Volume of Grafts

The actual volume of the grafts was measured, and 1 cm^3 of the liver was estimated at 1 g (*8*). The error ratio as a measure of the difference was evaluated according to the following formula: error ratio (%)=$|E-A|/A\times100$, where E is the estimated volume of the graft (mL), and A is the actual volume of the graft (mL).

Other Statistical Analysis

Data was expressed as mean±SD. The statistical analysis was performed using Student's t test where $P<0.05$ was considered significant. A stepwise regression analysis was performed for creating the new formula. $F>4.0$ was considered to be statistically significant.

RESULTS

New Formula for Estimating Left Hepatic Graft Created Using Stepwise Regression Analysis

The characteristics of both the donor and the graft in the initial 20 LDALTs and the other 41 LDALTs are summarized

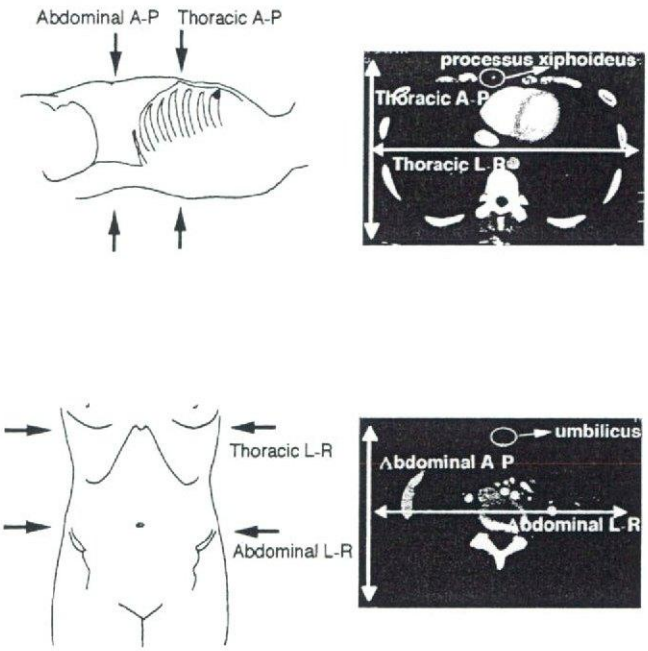

FIGURE 1. Location for the measurement of the variables such as (1) thoracic A-P (cm), 2) thoracic L-R (cm), (3) abdominal A-P (cm), and (4) abdominal L-R (cm) (*arrow*) using two-dimensional computed tomography (2D-CT). A-P, distance from anterior to posterior sides; L-R, distance from left to right sides.

in Table 1. There appears to be no significance for the variables of age, height, weight, thoracic A-P and L-R diameter, abdominal A-P and L-R, and actual volume between the initial 20 LDALTs and the other 41 LDALTs.

The result of the stepwise regression analysis in the initial 20 LDALTs is shown in Table 2. In the stepwise regression analysis, an F value was associated with the improvement in how well the model fits the data compared with the model.

TABLE 1. Characteristics of donor and graft in the initial 20 and the other 41 LDALTs

Factors	Initial 20 LDALTs, mean±SD (range)	Other 41 LDALTs, mean±SD (range)
Age (yr)	34.8±12.1 (21–56)	36.2±11.3 (20–65)
Height (cm)	168.3±7.0 (150.0–180.0)	166.1±8.8 (147.0–182.0)
Weight (kg)	61.5±11.1 (42.0–83.0)	64.4±15.2 (37–90)
Thoracic A-P (cm)	20.8±2.7 (16.3–25.7)	21.3±3.0 (16.1–26.8)
Thoracic L-R (cm)	29.7±2.3 (26.1–32.6)	30.3±2.7 (23.5–35.6)
Abdominal A-P (cm)	17.7±2.6 (14.8–23.2)	19.1±3.3 (12.2–25.4)
Abdominal L-R (cm)	27.7±3.0 (22.3–32.7)	28.9±3.5 (21.6–34.7)
Actual GV (g)	414.5±83.5 (260–620)	459.9±81.4 (320–630)

LDALT, living-donor adult liver transplantation; A-P, distance from anterior to posterior side; L-R, distance from right to left side; GV, graft volume.

TABLE 2. Outcome of stepwise regression analysis in initial 20 LDALTs

Variables	Regression coefficient	F value
Weight (kg)	7.734	137.1
Thoracic L-R (cm)	−12.62	15.26
Constant	313.4	22.02
Abdominal A-P (cm)	0.403	3.095
Abdominal L-R (cm)	0.201	0.675
Height (cm)	0.157	0.404
Thoracic A-P (cm)	0.016	0.004

F value>4.0 is statistically significant.

LDALT, living-donor adult liver transplantation; L-R, distance from left to right side; A-P, distance from anterior to posterior side.

Therefore, an F value corresponds to a *P* value in this model, and the variable enters into the formula when the corresponding F value is greater than 4.0 in this model (*11*). On the basis of the result, a new predictive formula (Kyudai formula) for an extended left-lobe graft was derived as follows: graft volume (mL)=313.4+7.7×weight (kg)−12.6×thoracic L-R (cm). F>4.0 was considered to be statistically significant ($R=0.966$, $R^2=0.933$, $P<0.0001$).

The estimated graft volume using the new formula in the other 41 LDALTs ranged from 289 to 584 (mean±SD 427±87, median 396) mL. The relationship between the actual volume of the grafts and the estimated volume of the grafts using the new formula in the other 41 LDALTs was linear: $y=173.931+0.67x$ ($R^2=0.518$, $P<0.0001$) (Fig. 2A).

Relationship between Actual Volume of Grafts and Estimated Volume of Grafts Using 2D-CT or 3D-CT

Estimated graft volume using 2D-CT ranged from 268 to 657 (mean±SD 472.9±87.4, median 465) mL. The relationship between the actual volume of the grafts and the estimated volume of the grafts using 2D-CT in the other 41 LDALTs was linear: $y=221.69+0.504x$ ($R^2=0.293$, $P=0.0003$) (Fig. 2B).

Estimated graft volume using 3D-CT ranged from 253 to 621 (mean±SD 460±93, median 446) mL. The relationship between the actual volume of the grafts and the estimated volume of the grafts using 3D-CT in the other 41 LDALTs was also linear: $y=199.091+0.567x$ ($R^2=0.421$, $P<0.0001$) (Fig. 2C).

Evaluation of Difference between Actual and Estimated Graft Volumes Using New Predictive Formula, 2D-CT, and 3D-CT

The error ratio for the new predictive formula was better (10.8±9.5%) than that of the conventional volumetry by 2D-CT (16.3±10.1%) or 3D-CT (13.5±10.6%) in the other 41 LDALTs. The new formula revealed a significantly more precise volume of the graft than those measured by 2D-CT images ($P<0.05$) (Fig. 3). There was no significance between the error ratio of the volumetry using the new formula and 3D-CT ($P=0.18$).

DISCUSSION

Since the first adult-to-adult living related liver transplantation was performed in 1993 (*12*), the number of LDALTs performed has increased all over the world. The use of the right lobe as a graft has been increasingly successfully used (*3*, *13*); however, these grafts (especially those not including

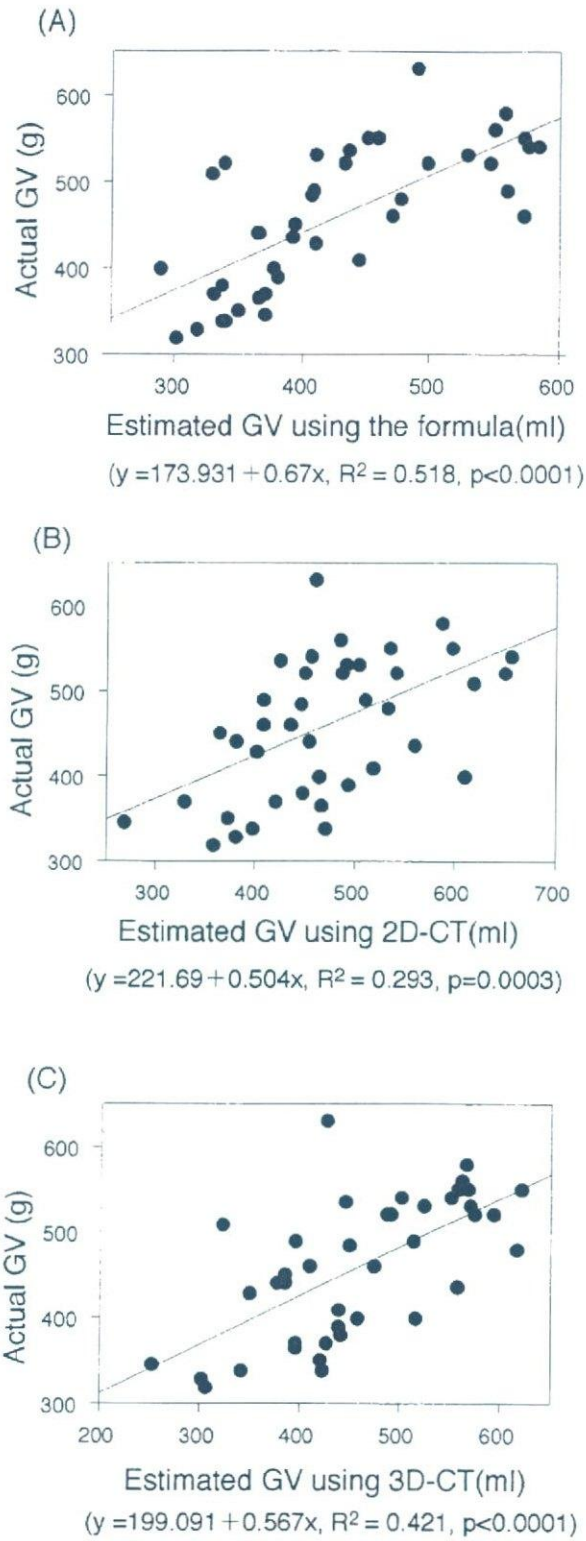

FIGURE 2. (A) Relationship between actual volume of the grafts and estimated volume of the grafts using the new formula y=173.931+0.67x (R^2=0.518, P<0.0001). (B) Relationship between actual volume of the grafts and estimated volume of the grafts using 2D-CT: y=221.69+0.504x (R^2=0.293, P=0.0003). (C) Relationship between actual volume of the grafts and estimated volume of the grafts using three-dimensional (3D-CT): y=199.091+0.567x (R^2=0.421, P<0.0001).

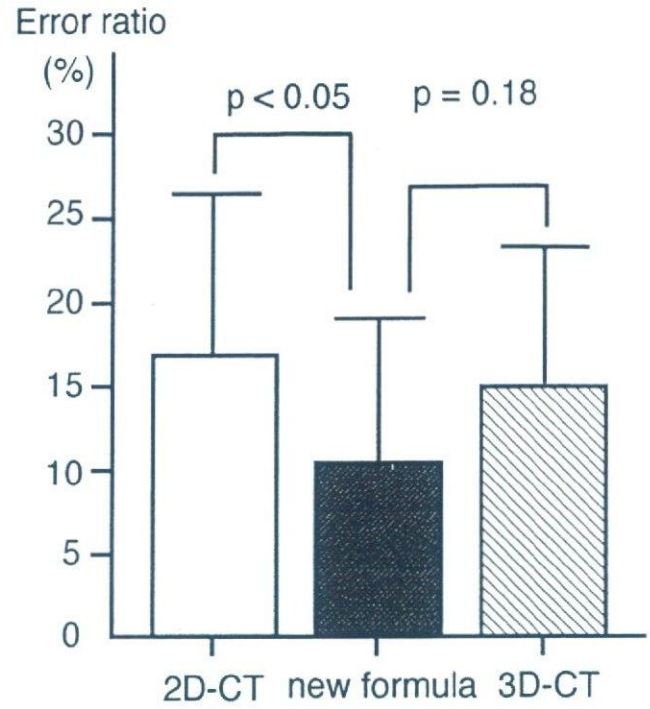

FIGURE 3. Error ratio of volumetry on the new formula, 2D-CT, and 3D-CT in the other 41 living-donor adult liver transplantations. The error ratio was 10.8±9.5% in the new formula, compared with 16.3±10.1% in 2D-CT or 13.5±10.6% in 3D-CT. The new formula revealed more precise volumes of the graft than those measured using 2D-CT imaging (P<0.05). There was no significant difference between the error ratio of the volumetry by the new formula and 3D-CT (P=0.18). The error ratio was calculated according to the following: error ratio (%)=|E−A|/A×100, where E is the estimated volume of the graft (mL) and Ais the actual volume of the graft (mL).

the middle hepatic vein) can potentially lead to graft congestion (*5*) and increases the technical complexity of the hepatectomy (*14, 15*). On the other hand, in left-lobe grafts, sufficient venous drainage is more likely to be present, and it may be the most ideal graft for both the donor and the recipient limited by size considerations.

We have reported a favorable outcome of LDALT using a left-lobe graft (*4, 5*). Although a major problem of small-for-size grafts often occurs when using a left-lobe graft in LDALT (*1–3*), it is possible to reduce the risks faced by both the recipient and donor if we can select the appropriate graft size of the left lobe. It has been reported that the minimum graft size for successful LDLT is approximately 30% (*16*). However, safety for graft size is thought to be approximately 40% (*4*). Thus, graft size is one of the most important factors for a favorable outcome for LDALT when using a left-lobe graft. Selecting the appropriate graft size is one of the most important aspects of a successful liver transplantation.

Currently, the method of graft estimation using 2D-CT (or 3D-CT) is popular and useful, but there is actually a difference between the actual graft volume and the estimated graft volume using 2D-CT or 3D-CT. First, there is a mismatch of the cutting line between the simulations and the actual hepatectomy. In the actual hepatectomy, the plane of dissection is set along the demarcation line, which

was marked by a temporary clamping of the hepatic artery. Second, when the graft volume is estimated using 2D-CT, the estimated volume includes the blood-vessel volume. Therefore, the actual graft volume is often smaller than the estimated graft volume.

In addition, it takes approximately 3 hours to estimate the graft volume using 2D-CT by scanning the CT film, and it takes approximately 4 hours to estimate the graft volume using 3D-CT by scanning of the CT film, compared with 10 minutes to estimate the graft volume using the new formula. Volumetry using 2D-CT and 3D-CT requires a special device such as zioM900 (Zio software inc., Tokyo, Japan) and a scanner (Epson GT-9500). Thus, the method of graft estimation using 2D-CT (or 3D-CT) has drawbacks, and therefore, we needed a more simple and accurate way to calculate left hepatic graft other than the method of graft estimation through the use of 2D-CT (or 3D-CT) in LDALT.

To minimize the difference between the estimated liver volume and the actual liver volume, we evaluated the initial 20 LDALTs using stepwise regression analysis, particularly using variables such as height, weight, the thoracic A-P and L-R, and the abdominal A-P and L-R. The reason we used such variables was that the size of the thorax was thought to be an important factor in estimating the liver volume, and these variables were thought to be correlated with liver volume. In fact, it is reported that liver volume is proportional to body surface area as calculated with height and weight (*8*). The formula created using stepwise regression analysis includes two variables, weight and thoracic L-R, and it revealed a significantly more precise volume of the graft than those measured using a 2D-CT image in the other 41 LDALTs ($P<0.05$). There was no significance between the error ratio of the volumetry using the new formula and 3D-CT in the other 41 LDALTs ($P=0.18$).

In conclusion, our new formula for predicting the volume of the left-lobe graft can estimate the actual graft volume more simply and accurately than conventional volumetry using 2D-CT. The formula appears, therefore, to be a very useful way to estimate the volume of the left-lobe graft in LDALT.

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特集：九州大学病院統合１周年記念企画

移植医療の現状

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はじめに

移植の歴史は半世紀に及ぶ．末期臓器不全の究極的治療法としての臓器移植はいまや定着し，世界的には日常診療の一部になっていると言っても過言ではない．本邦でも遅々として進まなかった移植医療も生体肝移植の導入を契機としてようやく開花しつつある．

本稿では，現在の移植医療，特に我々が長年取り組んできた肝臓移植の現状と問題点について概説する．

１．世界における臓器移植の歴史と現状

臓器移植の研究及び実験は腎移植にその端緒を発する．1902年のウイーンの外科医ウルマンがイヌの腎臓を別のイヌの首に移植し報告したのが最初である．1954年に米国のメリルとマレーらが一卵性双生児間の腎臓移植に成功し，生物学的に等しい個体である一卵性双生児の間では移植臓器が拒絶されないことが実証された．1961年にイギリスのカーンらがイヌの腎移植でアザチオプリンの免疫抑制効果を確認，1963年にマレーがヒトの腎移植に応用した．1963年にはスターツルが世界初の肝臓移植を胆道閉鎖症の患児に行った．同様に1963年に肺移植，1966年に膵臓移植，1967年に心臓移植が次々と行われた．しかし，拒絶反応の制御は困難であり一時臓器移植は急速に退潮した．

臓器移植の決定的なブレークスルーは新しい免疫抑制剤サイクロスポリンの発見である．これは1970年にスイスのサンド社の社員ボレルがノルウェーの土壌から採取したカビから分離した物質であり，1972年にその強力な免疫抑制作用を発見した．カーンが1978年に腎移植に，1979年に肝移植に応用した．1980年にスターツルが肝移植に，シャムウェイが心臓移植に応用し，１年生存率が80％と驚異的な成績を報告し，以後飛躍的に症例数が増加し臓器移植が末期臓器不全に対する外科治療として確立されるに至った．UNOS（United Network for Organ Sharing）の最新のデータによれば，2003年には全米で6,457例の脳死（又は心停止）ドナーからの臓器提供が行われ，5,263例（肝），9,765例（腎），1,381例（膵），111例（小腸），2,084例（心）の移植がそれぞれ行われた．

一方で移植待機患者の急速な増加に対して臓器提供が追いつかず，臓器不足が深刻化し大きな問題となっている．その解決手段として，健康な肉親などが臓器の一部を提供する生体腎移植，生体肝移植，生体肺移植などの方法が開発され，脳死ドナーの望めない日本などを中心に爆発的に症例数が増加している．本邦における生体肝移植の施行数は現在，年間400例以上通算でも3000例を超え，成人間生体肝移植も積極的に施行されるようになってきた．

一方，本邦においては1997年臓器移植法が施行されて以来2004年４月までの脳死肝移植数は計24例に過ぎないのが現状であり，脳死ドナーからの提供がほとんど機能していないことが我が国の移植医療の最大の問題点であるといえる．

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Current Status and Future Prospect of the Liver Transplantation : Kyushu University Hospital Experience

2．九州大学における肝移植の現状

当教室においては，1985年に移植研究室が発足した．当初肝臓・血管・門亢症の各研究室からのメンバーで構成され，発足直後より臨床肝移植を目的とした大動物実験を開始し，同時に国内の他の施設よりいち早くピッツバーグ大学やマウントサイナイ医科大学に継続的に教室員を派遣し臨床トレーニングを重ねた．

一方国内における移植医療のシステム作りとして，1988年に西日本臓器移植ネットワークを設立し，西日本地区における臓器移植医療の確立と定着のための基盤整備も行ってきた．移植施設だけではなくドナー病院の登録を進め，脳死ドナー発生からの移植シミュレーションを行った．

1990年には肝移植の技術を応用した体外肝切除を我が国で初めて施行し，九州大学医学部倫理委員会が1991年に生体肝移植を，1993年には脳死肝移植を承認後，1993年10月22日に我が国では実に29年ぶりとなる心停止ドナーからの肝移植を施行した(血液型不適合症例)．1996年10月14日には1例目の生体肝移植を施行．1997年5月2日には初の成人間生体肝移植を施行，いずれも成功をおさめた．1999年7月26日には本邦2例目のドミノ生体肝移植を行った．1997年10月脳死移植法案が可決され，2000年には脳死肝移植認定施設に認定された．2001年には九州大学における脳死肝移植が高度先進医療として認可された．そして2003年10月7日，大分県在住の34才男性に対し，九州初，本邦23例目となる初の脳死肝移植が行われた．術後経過は極めて順調で特に合併症なく術後29日目に無事退院となり，現在も元気に外来通院中である（図1，2，3に経過を示す)．

生体肝移植については，1996年10月14日に胆道閉鎖症の7才男児に対し1例目を施行して以来，2004年9月までの8年間に小児23例，成人141例の合計164例の生体肝移植を施行した．図4に示すごとく，ここ数年の症例，特に成人間生体肝移植の延びは際立っており，コンスタントに年間30例以上を施行するようになり年間症例数では京都大学，東京大学につぎいまや本邦第3位を占めるようになった．九州大学での生体肝移植はいまや日常診療のひとつになったといえる．

手技的にはほぼ確立されたといえる生体肝移植であるが，今後の課題として，脳死肝移植のさらなる推進，成人間生体肝移植の成績向上，進行肝癌に対する適応拡大・再発予防，C型肝炎再発予防法の開発，過小グラフトに対する対策，血液型不適合移植，胆管合併症（特に長期胆管狭窄）に対する対策などがあげられる．そこで最近急速に症例数が増加しつつあるC型肝炎と肝癌に対する肝移植の現状を概説する．

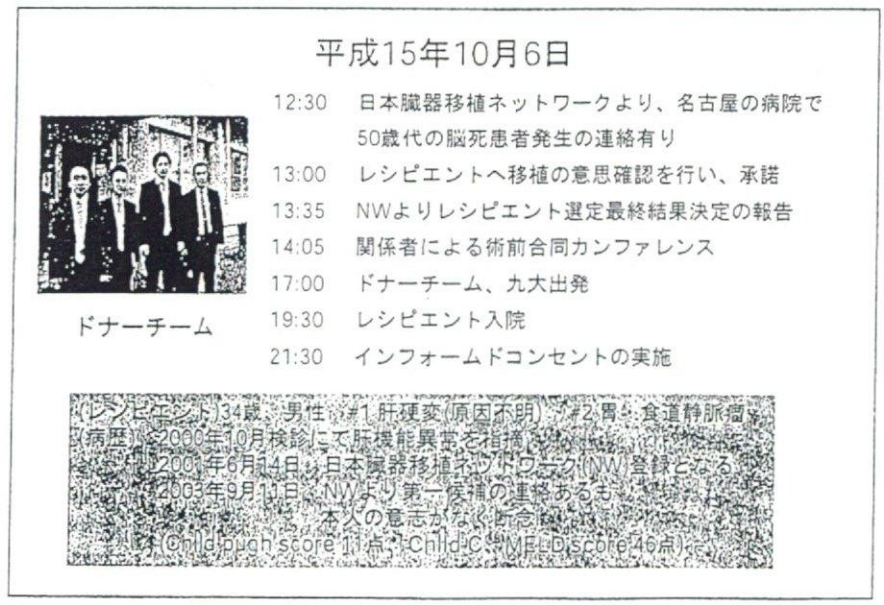

図1 九州大学初の脳死肝移植症例：第1日目

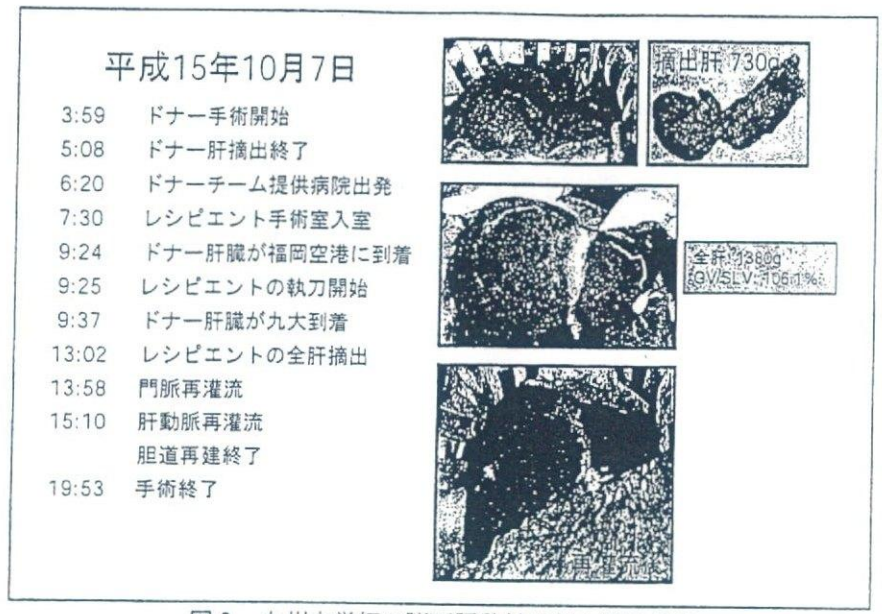

図 2　九州大学初の脳死肝移植症例：第 2 日目

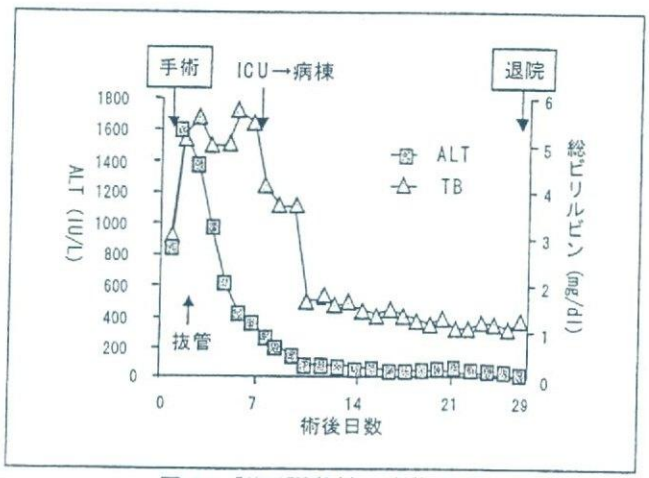

図 3　脳死肝移植の術後経過

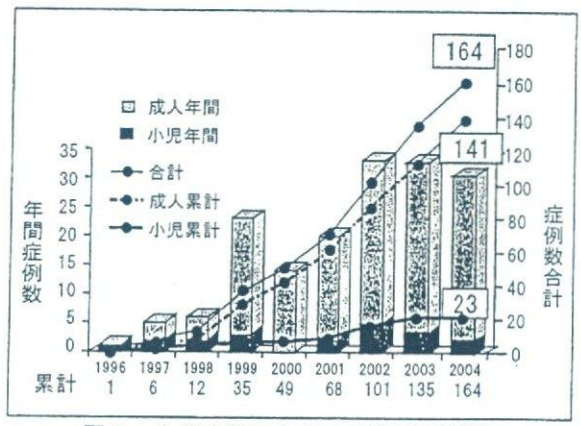

図 4　九州大学における肝移植症例数
(1996.10～2004.9)

（1）C 型肝炎に対する肝移植

アメリカでは C 型肝炎はアルコール性肝硬変と並んで，脳死肝移植におけるもっとも頻度の高い適応症であり，本邦でも今後症例数の増加が予想される．C 型肝硬変の移植ではほとんど全例で術後早期に HCV-RNA が検出され，ほぼ全例にウイルス学的再発は起こる[1]．その臨床経過は B 型肝炎再発にくらべて比較的緩徐である．最近 C 型肝炎患者の移植成績が以前に比較して悪化していることが報告され[2]大きな話題をよんでいる．移植後 10 年以上を追跡観察した最近の報告によれば，1，5，10 年の患者生存率は 84，68，68 %であった[1]．九州大学では 2004 年 9 月までに 164 例中 54 例（31.1 %）の C 型肝硬変症例（うち肝癌合併 41 例）に対して生体肝移植を施行している（図 5）．肝移植後の C 型肝炎再発予防には IFN と Ribavirin が一般的に用いられるが，ウイルス学的著効に至るのは 12～30%に過ぎず，C 型肝炎再発については未だ満足できる治療がないのが現状である．肝癌合併を含め C 型肝硬変症例 51 例の生存率は 1 年 79 %，2 年 67 %，3 年 67 %であり，ウイルス学的には術前 HCV RNA 陰性であった 2 例を除き，49 例に術後 HCVRNA を検出した．組織学的再発は 16 例（32 %）に認めた．累積再発率は 6 ヶ月 29 %，1 年 35 %，3 年 39 %であった．再発症例のうち 12 例では，インターフェロン α＋リバビリンにて治療を行い，ウイルス消失が持続したのは 5 例のみで，6 例は副作用（白血球数減少，全身倦怠感，貧血等）により治療を中断した．無効症例が 1 例であった．このように現在のところ C 型肝炎再発に対する治療に関し

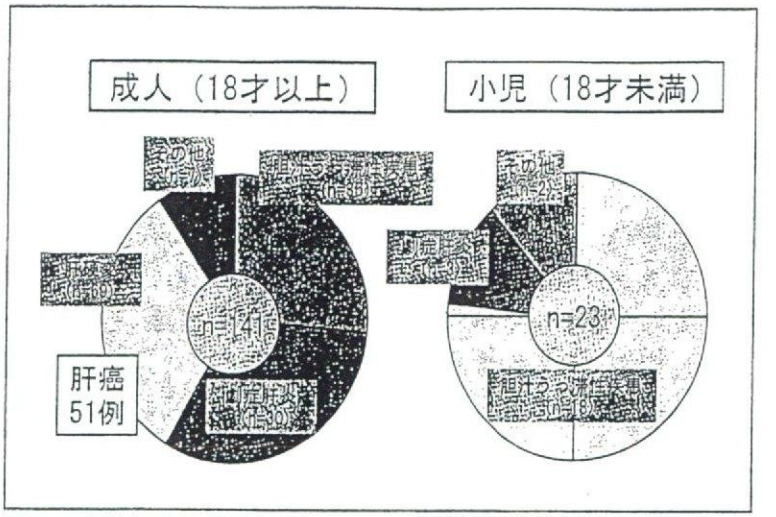

図5 九州大学における生体肝移植：適応疾患（164例：1996.10～2004.9）

ては満足な結果が得られていないのが現状である．

（2）肝癌に対する肝移植

肝癌に対する肝移植は，肝癌とともに肝癌の発生母地であるB型，C型肝硬変も同時に摘出し得ることからもっとも究極的な根治療法と考えられる．現在海外における肝癌に対する脳死肝移植登録基準は，(1)肝外，リンパ節転移がないこと，(2)血管浸潤がないこと，(3)単発：5 cm以下，多発：3 cm以下で3個以内（ミラノ基準[3]）を満足することである．

このような移植適応の厳格化により5年生存率は85％，無再発生存率は90％と良性肝疾患とほぼ同等の移植成績を示しており，我が国でも脳死登録の基準として，あるいは生体肝移植の保険適応基準として採用されている．

肝癌に対する生体肝移植においては健常ドナーからの臓器提供が必要なため適応基準をより厳格にすべきとの考えと，必然的に臓器提供は親族からに限定されるため双方がリスクを十分に理解した上でならより適応を拡大してもいいとの考えがある．現実的には我が国のほとんどの施設での適応は，肝移植以外の治療法で腫瘍がコントロール出来ず，肝外転移及び腫瘍血管への浸潤がない肝癌とされており，腫瘍径や腫瘍個数には制限を設けていない．

当科における肝癌への移植適応基準は肝外病巣がなく，肝内主要血管への明らかな腫瘍の侵襲を認めず，肝移植以外に有効な治療法が現存しない場合である．ただし，肝移植後の長期予後が他の治療法より明らかに上回ると予想される場合には個々の症例につき検討し適応を判断するとしている．

九州大学ではこれまで164例中50例（30.5%）の肝細胞癌に対する生体肝移植を施行した．背景にある肝硬変の原因としてはHCV 40例，HBV 6例，NonBNonC 4例であった．また術前のChild分類ではChildCが最多であったが，腫瘍が両葉，多発性に分布した症例等はChildAでも適応となる場合があった．このため，Stage IIIが大半を占めた．肝癌症例における1年，2年生存率は86.2％，68.4％であった．50例中7例に再発を認めた．

これまでは治療不能とされていた肝細胞癌も症例によっては肝移植によって根治させることが可能となってきた．今後はC型肝炎再発への対策等課題は多いものの保険適応となった現状を踏まえ，よりいっそう移植治療の必要性が高まるものと考えられる．

3．再生医療の現状と展望 —肝，肺について—

移植医療が急速に発展する中，細胞・臓器の供給不足，ドナー不足は深刻な問題であり，現在その新た

な細胞・臓器の供給源として，またそれに代替しうる治療として，幹細胞研究をはじめとする再生医療に大きな期待が寄せられている．

われわれ腹部外科・胸部外科での移植医療の領域においては，現実の医療となった肝移植や肺移植の見地からも，特に肝や肺の再生医学に注目するところである．胚性幹細胞（ES 細胞）や体性幹細胞からの肝や肺の細胞・組織への分化や，その発生におけるメカニズムに関する研究は近年飛躍的に進歩しているが，その成熟細胞への特異的な分化や組織の再構築に関しては未だ確立しておらず試験的なものも含めて臨床応用には至っていないのが現状である．

肝については，肝幹細胞とも考えられている oval cell や小型肝細胞の存在が示されており，これらから成熟肝細胞への分化が報告されている[4]．また ES 細胞から肝細胞への分化に関する研究も急速に進んでおり，肝の細胞レベルでの再生は可能となってきている．しかしながら，その特異的な分化誘導や組織の再構築，細胞数の獲得に関しては未だ確立しておらず，臨床応用までにはもう少し時間が必要と考えられる．

一方，肝のように求められる最低限の機能が細胞レベルでも良い臓器に比べ，肺は組織・臓器レベルでの高度な機能が要求されるため，その再生の実現は非常に困難と考えられる．この分野においては発生についての研究は多臓器同様，近年急速に発展しており，そのメカニズムの解明も進んでいるが，再生についてはその機能の複雑さもあってか，ES 細胞から分化した細胞集団に肺胞上皮特異的なサーファクタント C の産生を認めた報告[5]などはあるものの，具体的な再生の研究は始まったばかりであり今後の発展が切望される．

現在再生医療は，造血，血管，心臓などの一部の分野においてのみ臨床応用が実現しているが，再生医療が組織・臓器の機能障害や機能不全，欠損による疾患に及ぼすその恩恵は計り知れず，幅広い分野においてその実現に大きな期待が寄せられている．また同時にその研究，医療を進めていくうえでは，多くの社会的，倫理的な議論やコンセンサスが必須である．

おわりに

手技的な問題点はほぼクリアされたと思われる我が国の移植医療であるが，やはり脳死ドナーからの臓器提供が移植医療の本道であるのは疑いがない．今後，脳死法案の改訂などの基盤整備やさらなる啓蒙活動により，脳死ドナーの増加をはかることが，我が国の健全な移植医療の発展のためには必須であろう．

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症　例

C型肝硬変に対する生体肝移植後に急速な経過をたどり死亡した fibrosing cholestatic hepatitis の1例

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米村祐輔　島田光生*　吉住朋晴
武冨紹信　前原喜彦

ウイルス性肝硬変に対する肝移植は近年増加傾向にある．C型肝硬変に対する移植の問題点は移植後のC型肝炎の再発であり，術後1年以内に50～60%が組織学的に慢性活動性肝炎を再発し，術後5年で約20%が肝硬変に進行するとされている．C型肝炎の場合，肝炎の再発はほとんどが軽度であり，緩徐な経過が特徴とされている．一方，fibrosing cholestatic hepatitis（FCH）は組織学的に胆汁うっ滞，門脈周囲の線維化，肝細胞腫大，軽度な炎症などの特徴を認め短期間で肝硬変に進行し，主にB型肝硬変における移植後の肝炎再発形式とされている．近年，C型肝硬変に対する移植後にもFCHが認められ，近年増加傾向にあるとされている．今回われわれはC型肝硬変に対する生体肝移植術後に高ビリルビン血症を認め組織学的に急速な線維化をきたし術後233日目にグラフト機能不全で死亡したFCH症例を経験したので報告する．

索引用語：生体肝移植，C型肝炎，fibrosing cholestatic hepatitis(FCH)

緒　言

C型肝炎に対する肝移植後の問題点は高率に肝炎が再発することである．一般に，C型肝炎の再発は軽度で経過が緩徐であるとされている[1)~3)]．一方，fibrosing cholestatic hepatitis（FCH）は急速に肝硬変へと進行する病態であり，主にB型肝炎に対する移植後に認められる．しかしながら稀ではあるが近年C型肝炎に対する移植後のFCHが報告されている[3)4)]．当科では，HCV陽性患者に対してこれまでに生体肝移植を51例施行しており，今回われわれは生体肝移植術後に，FCHを発症し急速な経過をたどった症例を経験したので報告する．

症　例

症例：40歳，男性．

主訴：全身倦怠感，腹部膨満．

既往歴，家族歴：特記すべき事項なし．

現病歴：1997年，腹部膨満を自覚し，近医を受診した際腹水を認めた．HCV陽性および肝硬変を指摘され，上部消化管内視鏡にて食道静脈瘤を認め内視鏡下静脈瘤結紮術を施行された．その後，利尿剤の内服にて経過観察されていた．2001年8月，再び腹部膨満感が出現．近医入院の上，腹水コントロールを行い3週間で退院した．2002年10月，腹水コントロール目的で再入院．精査にて著明な肝機能の低下を認めた．11月に感冒を契機に肝機能が悪化し，生体肝移植目的で当院を紹介され，12月10日，適応評価目的にて当科入院となった．

入院時現症：黄疸・腹水著明，脾腫あり，肝性脳症I度．

入院時検査所見：血液型AB型Rh(+)，〈血算〉WBC 17,380/mm³，RBC 292/mm³，Hb 10.3g/dl，Ht 29.0%，Plt 13.3万/mm³，〈生化学〉TP 6.1g/dl，Alb 3.2g/dl，BUN 51mg/dl，Cr 1.81mg/dl，Ccr 29.0ml/min，TB 11.1mg/dl，DB 8.1mg/dl，TTT 6.8KU，ZTT 13.0KU，AST 94IU/l，ALT 49IU/l，LDH 242IU/l，ChE 15IU/l，Na 125mEq/l，K 5.1mEq/l，Cl 95mEq/l，T-chol 43mg/dl，TBA 241.5μmol/l，NH_3 42μg/dl．〈凝固系〉PT 16.8 (11.2) sec，PT% 46%，HPT 35%．〈ウイルスマーカー〉IgM-HA(−)，HBsAg(−)，HBsAb(−)，HBeAg(−)，HBeAb(−)，

2004年5月25日受付　2004年8月31日採用
〈所属施設住所〉
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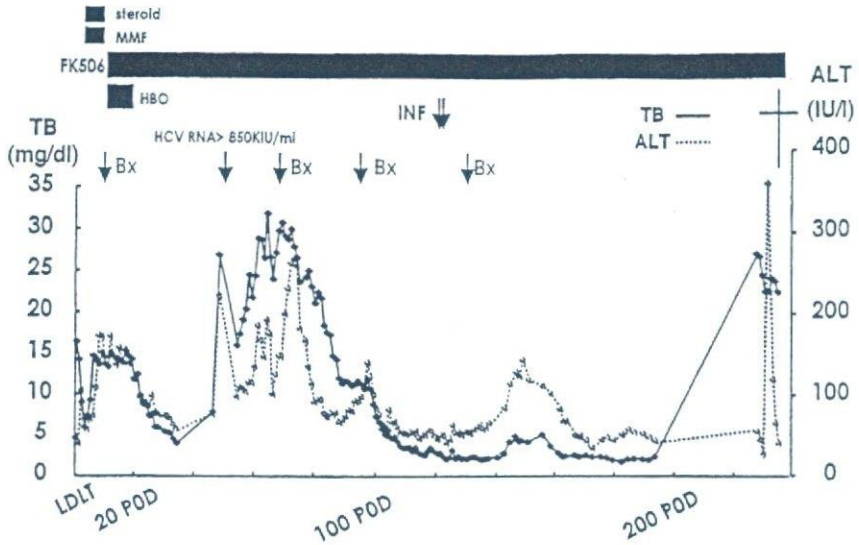

図1　肝移植後の経過(MMF：ミコフェノール酸モフェティル，HBO：高圧酸素療法，INF：インターフェロン，Bx：肝生検，TB：総ビリルビン，LDLT：生体肝移植，POD：術後日数)

HBcAb(−)，HBV DNA(−)，HCV Ab(+)，AMA(−)，ANA(−)．〈腫瘍マーカー〉AFP 6.2ng/ml，PIVKA 17mAU/ml．

入院時画像所見：肝萎縮，著明な脾腫，大量の腹水あり．腫瘍性病変やシャントは認めず．

手術：2003年1月7日，39歳の実弟(A型 Rh+，適合)をドナーとして生体肝移植術を施行．拡大左葉＋尾状葉グラフト，グラフト重量370g，GV/SLV＝33.6%，GRWR＝0.73%，手術時間：12時間11分，出血量：11,486g．

術後経過：免疫抑制剤は，ステロイド，ミコフェノール酸モフェチル，バシリキシマブの3剤で導入．HCV陽性のためステロイドは1週間で中止し，以後FK 506の投与のみとした(図1)．術後7日目よりビリルビン，トランスアミナーゼの上昇を認め臨床的にsmall-for-size graft syndromeと診断し，高圧酸素療法を開始した．ビリルビン(2〜3 mg/dl)，トランスアミナーゼが正常化し術後34日目に退院となった．術後52日目より再度ビリルビン(15.9mg/dl)，トランスアミナーゼの再上昇を認めた．術後55日目のHCV RNAは検出限界の上限を超えており(HCV RNA＞850KIU/ml)，C型肝炎の再発が疑われた．術後76日目の肝生検(術後3回目)にて，門脈域周囲の偽胆管の増生と，軽度の炎症細胞浸潤，中心静脈周囲の胆汁うっ滞とうっ血および軽度の肝細胞の腫大を認め，軽度の肝炎の診断にて肝庇護剤の投与を施行(図2)．その後，ビリルビン，トランスアミナーゼは低下したが再上昇を認めたため術後97日目に肝生検(術後4回目)を施行した．門脈域周囲の偽胆管増生，炎症細胞浸潤，中心静脈周囲の肝細胞の腫大，脂肪化，好酸性小体を認め，C型肝炎の再発に伴う肝炎の所見であった(図3)．その後トランスアミナーゼは軽度上昇程度まで下がったが，白血球減少のためINF＋リバビリン療法が施行できず低容量IFN療法(300万IU×1/day)を施行した．しかし，白血球減少が進行し，2回施行後に中止した．術後135日目(5回目)の肝生検では，門脈域周囲の偽胆管増生と炎症細胞浸潤を認め，マッソン・トリクローム染色では架橋線維化を認めた(図4)．その後，腹水の増加を認め肝不全となり術後233日目に死亡した．死亡時の肝組織は広範性壊死を伴った肝硬変の所見であった(図5)．

考　察

C型肝硬変症例に対する肝移植の問題点は，移植後の肝炎の再発である．術後1年以内に50〜60%が組織学的に慢性活動性肝炎を呈し，術後5年で約20%が肝硬変に進行することが知られている．長期的には肝炎再発はほぼ全例に起こると考えられている[1)〜3)]．一方，本症例のように，移植後急速に肝硬変へと進行するFCHは本来肝移植後のB型肝炎の再発形式と考えられ，急速に肝硬変へと進行し肝不全に至る肝炎として1991年にDaviesら[4)]によって報告されている．組織学的には胆汁うっ滞と門脈域周囲から小葉内へと進展する線維化と胆汁うっ滞を特徴とする肝炎であるが，炎症細胞浸潤は比較的軽度とされている[4)]．血清学的に

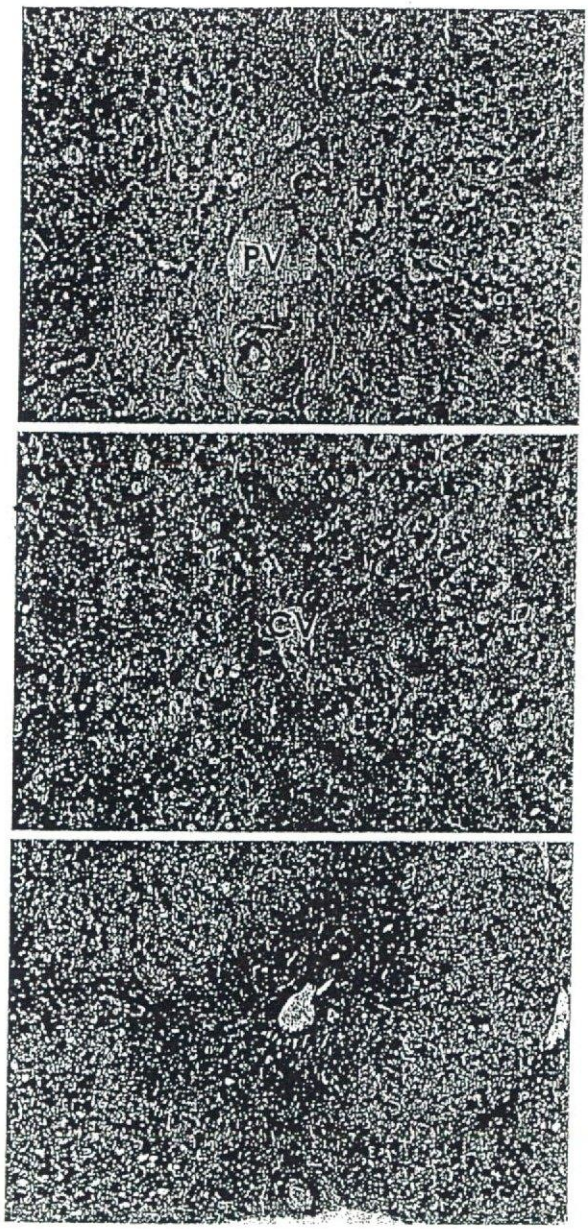

図2　肝生検病理組織標本(術後76日目)：a)門脈域辺縁部での偽胆管増生，炎症細胞浸潤は軽度(H-E染色，×100)．b)中心静脈周囲での胆汁うっ滞，うっ血，軽度の肝細胞の腫大(H-E染色，×100)．c)門脈域から小葉内へ進展する網目状の線維化(Masson's trichrome染色，×40)．

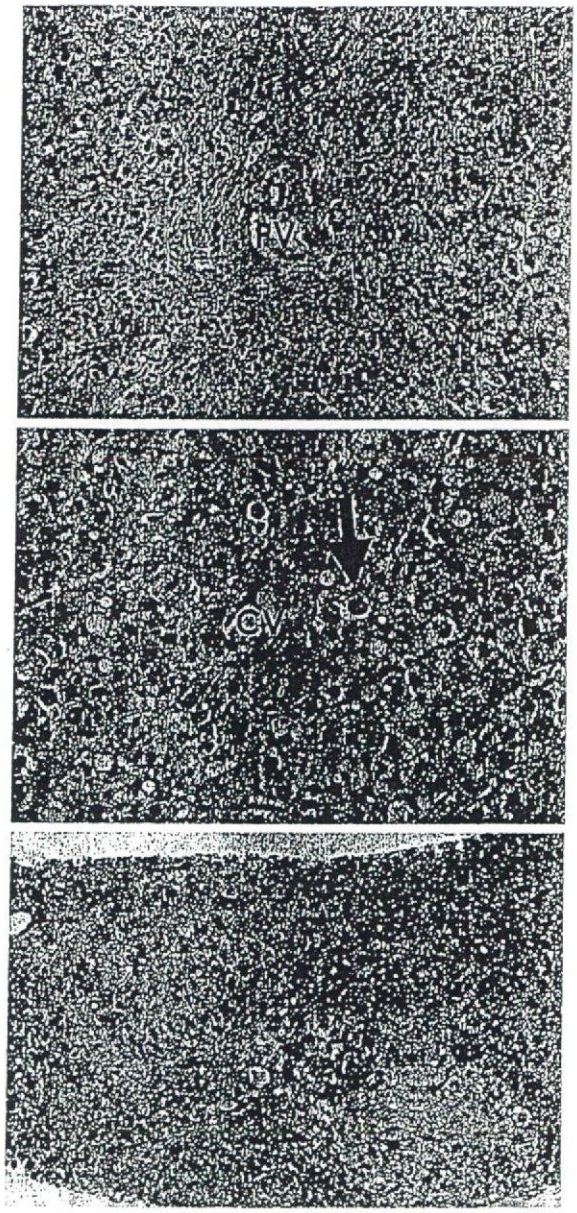

図3　肝生検病理組織標本(術後97日目)：a)門脈域周囲での偽胆管増生，炎症細胞浸潤は強い(H-E染色，×100)．b)中心静脈周囲での肝細胞の腫大，脂肪化，好酸性小体(H-E染色，×100)．c)門脈域から小葉内へ進展する線維化の増強(Masson's trichrome染色，×40)．

は肝機能低下に伴うプロトロンビン時間の延長，アルカリフォスファターゼの上昇，比較的低い値のALTである[5]．臨床的特徴は免疫抑制状態，つまり臓器移植後での免疫抑制剤投与下や，HIV陽性患者において発症しやすく，急速に肝の線維化が進行し肝硬変に至り肝不全に陥ることである[6)~9)]．FCHはHBV陽性患者における肝移植後の肝炎再発時の特徴とされてきたが，最近FCHが臓器移植後のHCVの再発の際に認められ注目されている[10)11)]．特にHCV陽性患者のFCHは，腎もしくは肝移植後の1～9％に認められその頻度は最近増加傾向にあるといわれている[3)12)]．HCVにおけるFCH発症にも免疫不全状態が関与し

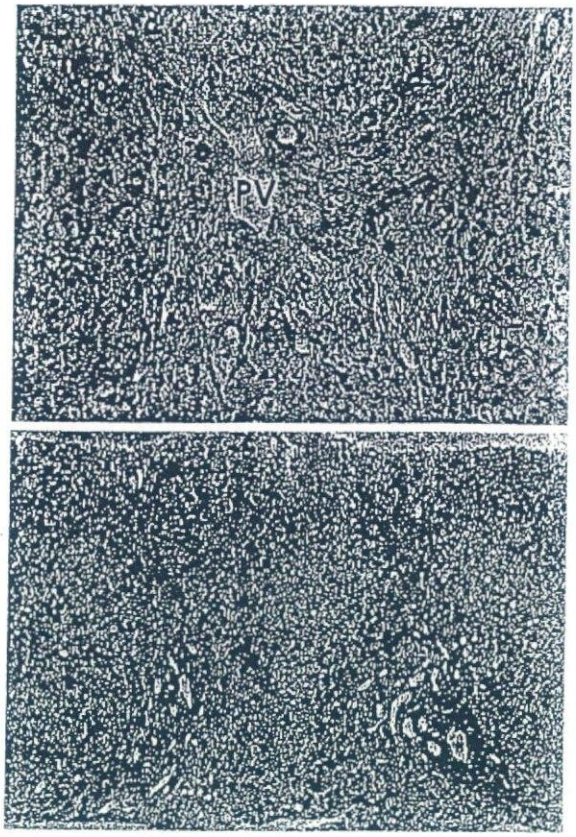

図4　肝生検病理組織標本（術後135日目）：a）門脈域周囲での偽胆管増生，炎症像(H-E 染色，×100)．b）架橋線維化（Masson's trichrome 染色，×40)．

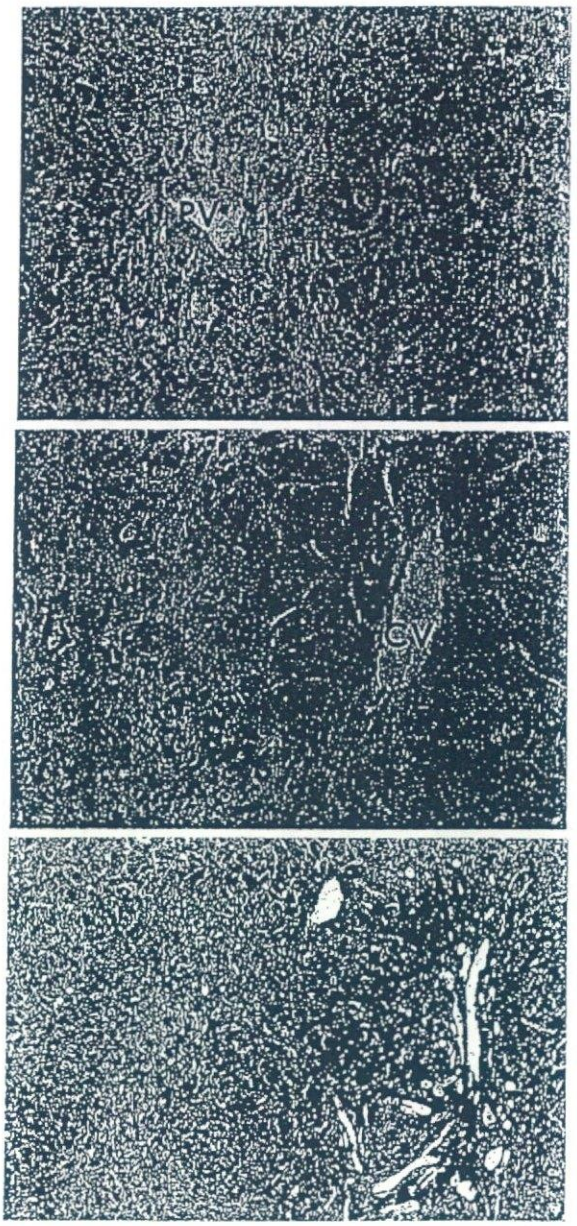

図5　死亡時肝病理組織標本（術後233日目）：a）門脈域周囲での偽胆管増生，軽度～中等度のリンパ球を主体とした炎症細胞浸潤(H-E 染色，×100)．b）広範性肝壊死，高度の線維化（H-E 染色，×100)．c）小葉構築を破壊する高度の線維化（Masson's trichrome 染色，×40)．

ており，HBV と同様に臓器移植後，HIV 陽性患者にも認められ，拒絶の治療をはじめ，CMV 感染や胆汁鬱滞がリスクファクターである[13]．FCH の治療として再移植が挙げられるが，再移植後も再発することも多くドナーの有無の問題があり実際には行われないのが現状である[14]．したがって，早期発見が重要であり，肝機能が低下する前に IFN＋リバビリン療法を施行することでグラフト不全を回避できる可能性がある[15]．今回，われわれが経験した症例では，HCV RNA 検査では術後早期（術後55日目）に高値となり，組織学的にも術後76日目の肝生検で既に，FCH を示唆する所見を認めた．しかし，肝機能不良のため IFN＋リバビリン療法が施行できず，低容量 IFN 療法を試みるも開始3日目で好中球減少をきたし治療継続困難であった．C 型肝硬変に対する肝移植術後は肝炎の再発は必発であり，FCH のように急速にグラフト不全をきたす症例もあるため，早期診断には定期的な肝生検と予防的な IFN＋リバビリン療法の施行が安全かつ効果的に行えるプロトコールの作成が今後の課題である．肝炎再発の予防や再発後の効果的な治療法が切望される．

結　語

HCV 陽性患者における生体肝移植術後に FCH を認めた場合，早期にグラフト不全をきたす可能性があることに十分留意すべきである．したがって，FCH に