Table 23.1 Proposed standard and extended criteria donors

Donor data	SCD	ECD
Age	0–50 years	50–60 years
Donor–recipient size match	DRWR and DRHR compatible	Reduced graft
ICU stay	<1 week	1–2 weeks
BMI	<28	28–30
CPR	<10 min	>10 min
Sodium	<155 mEq/L	155–165 mEq/L
Blood group	Identical	Compatible

CPR cardio pulmonary resuscitation, *DRWR* donor–recipient weight ratio, *DRHR* donor–recipient height ratio, *ICU* intensive care unit

the "marginal" intestinal graft. However, as intestinal transplantation has become increasingly common, the "luxury of selectiveness" in graft procurement has diminished greatly, thereby requiring consideration of extended donor criteria in intestinal transplantation, similar to the evolution of transplantation of other solid organs.

23.1.1 Japanese Experience

We performed a retrospective analysis of 12 deceased donors from whom 12 isolated intestinal grafts were recovered and successfully transplanted in Japan between January 2001 and December 2012. Data were extracted from the anonymized database of the Japan Organ Transplant Network. Data were analyzed for every donor, including recipient demographics and initial graft function (Table 23.1).

23.2 Definition

An accepted definition of marginal intestinal donor has not been definitively established. Among the most prominent donor characteristics that may influence graft survival include older age, cardiopulmonary arrest, viral status, graft size mismatch, and elevated liver function tests (LFTs). More long-term determinants of poor patient and graft survival are crossmatch positivity and donor-specific antigen positivity.

23.3 Viability and Outcome

23.3.1 Donor Age

The ideal donor for intestinal transplantation is younger than 50 years [4–7]. Donors older than 50 years are considered extended criteria donors. Some programs reported marginal donor organs have been used successfully [4, 6].

The Japanese experience has been similar. The mean donor age was 37 years old, with two donors over the age of 50 [8]. Among living donors, the maximum age allowed was 60 years [9]. Marginal donor organs should not be discarded.

23.3.2 Graft Size Match

Weight is an important factor in donor selection. The donor should be similar in size or smaller than the recipient since the recipient's abdominal cavity is often small due to extensive resection of the intestines. Graft sizes 25–50 % smaller than the recipient are generally preferred [4, 10–13]. Size reduction or adaptation of the graft may be possible to overcome recipient size mismatch [4, 14, 15]. Larger donor organs may be implanted since children with end-stage liver disease often have abdominal distention. It is also possible to decrease the length of donor bowel in patients receiving an isolated small bowel transplant and decrease the size of the liver graft in those requiring a larger composite graft. Due to shortages in pediatric donors, donor size mismatch is not an absolute exclusion. A high body mass index (BMI) may indicate a high mesenteric fat content, which can cause graft size mismatch with hardness of mesenteric fat in cold solution. A study allows BMI 28 kg/m^2 [16]. General surgical experience indicates that a high BMI ($\geq$30 kg/m^2) may increase the risk of surgical complications.

However, a BMI $\geq$30 may not affect graft quality, and it is not an absolute contraindication to living donation [9]. There is no data supporting a clear cutoff for donor BMI.

23.3.3 Cause of Death

The cause of the donor's death is not related to exclusion criterion [17]. However, death due to abdominal trauma is not preferred because of the potential for intestinal injury or contamination. Direct abdominal injury or severe deceleration trauma should be considered contraindication for intestinal donation. Extra-abdominal trauma is acceptable. In our experience, 75 % of intestinal donation had brain-related causes of death, such as head trauma or cerebrovascular accident [8].

23.3.4 Cardiopulmonary Arrest

Previously hemodynamically unstable donors are not preferred because the intestine is very sensitive to ischemia. Consequently, potential donors who are managed on high doses of vasopressors, those with extended periods of hypotension, or those who experienced cardiac arrest or cardiopulmonary resuscitation are excluded. Resuscitation has been associated with overall poor donor quality [18].

Neurogenic and hormonally driven splanchnic vasoconstriction may result in clinically relevant intestinal ischemia. Intestinal ischemia may affect graft viability by breaking down the intestinal mucosal barrier. Ischemia may promote leukocyte migration into the intestinal graft, resulting in early acute rejection and increasing the risk of bacterial translocation and infection.

Outcomes of grafts retrieved from donors with and without cardiac arrest used in isolated intestinal transplant and multivisceral transplant have been compared. The mean duration of cardiac arrest and subsequent cardiopulmonary resuscitation (CPR) was 19.3 ± 12.7 min. Compared with donors who did not undergo CPR, there were no significant differences in outcome parameters such as operative time, blood use, duration of mechanical ventilation, length of hospital stay, time to enteral independence, rejection, enteric bacteremia, and survival [17].

These results were consistent with our experience. All patients who received graft from the cadaveric donor with CPR more than 10 min survived. The duration of the CPR ranged from 35 to 47 min [8].

A donor history of cardiac arrest should not automatically exclude the use of the intestinal graft for transplantation.

23.3.5 Inotropic Support

In addition to potential donors who underwent CPR, donor candidates with high doses of vasopressors are excluded. There is concern that high doses of vasoactive medications may damage organs through visceral vasoconstriction. The United Network for Organ Sharing (UNOS) data has previously shown that donor organs subjected to prolonged hypotension have no significant increase in posttransplantation graft loss.

Fischer-Frohlich et al. reported that 31 % of donors were hemodynamically unstable immediately after hospital admission, but subsequently recovered [16]. Initial hemodynamic instability was treated with vasopressors and inotropic agents (e.g., norepinephrine >0.1 μg/kg/min supplemented by dobutamine >10 μg/kg/min) as well as transfusions as necessary until proper circulation was achieved. While there is concern that high doses of vasoactive medications may damage organs through visceral vasoconstriction, all unstable donors in our series recovered hemodynamically, and their organ function recovered subsequently as well. Short-term use of a high dosage of vasopressors in donors unstable upon hospital admission does not exclude intestinal donation.

In the Japanese experience, the most common cause of death was head trauma. Dopamine was used in ten cases (83 %) as a vasopressor, with a mean maximum dose of 10.7 μg/kg/min. The highest maximum dose was 21.2 μg/kg/min. Three donors required more than 15 μg/kg/min of dopamine. All recipients from donors who received high doses of dopamine survived in our experience [8].

Donors who received high doses of vasopressors are not excluded but are considered marginal donors. The question of which catecholamines, and at what doses, are detrimental to organ procurement remains unanswered.

23.3.6 Viral Status

Donor infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) confirmed by blood tests remains a contraindication to intestinal donation [9].

Cytomegalovirus (CMV)-positive donors should not be considered for CMV-negative recipients because of the significantly higher mortality rate in this group [19]. This guideline should be strictly adhered to in isolated intestinal transplants and whenever possible with other types of grafts.

However, with the development of medications and diagnostic tests for CMV, early diagnosis of CMV infection and prompt preemptive therapy have significantly reduced the risk of CMV disease. Even with the nearly unrestricted use of CMV-positive donors, there have been no CMV-associated deaths among recipients [20].

In Japan, most donors are CMV-positive; however, no CMV-related deaths have been reported.

23.3.7 Intensive Care Unit Stay

Intensive care improves the quality of donor organs [21]. A report recommended that intensive care unit (ICU) stays longer than 1 week should not exclude intestinal donation [17]. In our experience, the mean ICU stay was 8 days, and 6 patients (50 %) stayed longer than 1 week [8]. Long ICU stay is also an acceptable extended criterion. Enteral nutrition should be started as soon as possible after admission to the ICU, as recommended by guidelines for enteral nutrition.

23.3.8 Laboratory Values

The sodium level represented the most important parameter influencing the acceptance of intestinal grafts. Serum sodium should be kept within normal range [6, 7, 21]. However, in our experience the mean sodium level was 145 mEq/L, with three patients with a sodium level greater than 150 mEq/L [8]. Other study allows 155 mEq/L sodium level [16]. Sodium in the range of 155–165 mEq/L should be considered an extended criterion. LFTs may show intestinal ischemia; the LFT trend is important. LFTs trending towards the normal range may indicate recovery, while increasing values may represent intestinal ischemia. Following CPR, aspartate transaminase (AST), alanine transaminase (ALT) twice the upper limit of the reference range, as well as creatinine and bilirubin in the reference range had no impact on the outcome of intestinal transplantation [17]. CRP was elevated in our experience, with a mean value of 18 mg/dL [8].

23.3.9 ABO Compatibility

Identical ABO blood type is preferred [12]. Some centers might occasionally decline offers of intestines from nonidentical ABO compatible donors in favor of waiting for an ABO-identical offer. Pediatric centers, however, receive many fewer offers and thus more frequently accept nonidentical but compatible donor intestines if the donor weight and age are favorable [22].

23.3.10 Human Leukocyte Antigen Typing Crossmatch

Ideally, donors with a positive lymphocytotoxic crossmatch should be avoided; however, there is usually a prolonged wait for crossmatch results, which could endanger the graft by extending the cold ischemia time. Pretransplant donor-specific antigen in the intestinal graft can be a risk factor for immediate (hyperacute) but potentially reversible, antibody-mediated rejection. Thus, pretransplant donor-specific antigen and crossmatch results are critical components to be considered in patients awaiting or undergoing intestinal transplantation [23].

23.4 Basic Research

Graft viability prior to transplantation has an important influence on the outcome. Preservation damage is one of many essential factors that can affect the quality of the intestinal graft.

Intestinal graft quality with University of Wisconsin solution (UW), histidine–tryptophan–ketoglutarate (HTK), Celsior, and Polysol has been compared in rats. HTK and Celsior showed benefits versus UW [24].

To facilitate comparing the results using various solutions, adenosine triphosphate (ATP) precursors such as amino acids are added during preservation in order to improve viability. Acidic end products of the tricarboxylic acid (TCA) cycle like ammonia must be buffered. Regarding amino acid supplementation, only 4 % amino acid concentration showed better results than UW [25].

The intestinal lumen is a target for preservation. During ischemic preservation, tissue edema is believed to originate from the lumen, along with increased permeability. Furthermore, the lumen is potentially contaminated by bacteria. Celsior seems to be the best luminal preservation solution [26].

Rapidly progressing mucosal breakdown limits intestinal preservation time to under 10 h. Recent studies indicate that intraluminal solutions containing polyethylene glycol (PEG) alleviate preservation injury of intestines stored in UW. A customized intraluminal PEG solution reduces intestinal preservation injury by improving several major epithelial characteristics without negatively affecting brush-border enzymes or promoting edema [27].

Hypothermic machine perfusion generates a flow of recirculating cold preservation solution. For the intestine, cold storage is assumed to be superior to hypothermic machine perfusion due to possible pressure-induced vascular injury. However, the comparison of two pulsatile perfusion systems with cold storage and with a combination of 6 h of cold storage plus 18 h of pulsatile perfusion demonstrated a better outcome after machine perfusion preservation in a canine model [28].

Several intricate oxygenation techniques have been attempted. A 2-layer oxygenated perfluorocarbon/UW method was evaluated for canine preservation and intestinal transplantation. All dogs in the 2-layer oxygenated perfluorocarbon/UW group survived. Graft histology and absorption capacity was similar to non-preserved grafts [29].

23.5 Summary

Extended criteria for donation of intestinal transplant grafts include donor age 50–60 years, CPR longer than 10 min, ABO compatible, ICU stay from 1 week up to 2 weeks, high doses of vasopressors, elevated LFTs, sodium level 155–165 mEq/L, and a compatible donor–recipient size match. Any extended criteria donor graft should be considered potentially suitable for the patients on long waiting lists and not be discarded without seeking timely intestinal transplantation.

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Establishment of Educational Program for Multiorgan Procurement From Deceased Donors

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ABSTRACT

Introduction. Multiorgan procurement is not an easy procedure and requires special technique and training. Since sufficient donors are not available for on-site training in Japan, establishment of the educational program for multiorgan procurement is mandatory.

Materials and methods. Development of e-learning and simulation using pigs are our main goals. E-learning contains three dimensional computer graphic (3DCG) animations of the multiorgan procurement, explanation of both donor criteria and procurement procedure, and self-assessment examination. To clarify the donor criteria, the risk factors to 3-month survival of the recipients were analyzed in 138 adult cases of liver transplantation. The 3DCG animation for liver procurement was developed, which was used in the lecture prior to the simulation on August 10, 2013. The results of the examination after this lecture (exam 2013) were compared with the results after the lecture without using animation in 2012 (exam 2012). The simulation was performed by 97 trainees divided into 9 teams, and the surveys were conducted.

Results. The risk factors for early outcome of the recipients were cold ischemia time ($\geq$10 hours), Model for End-stage Liver Disease score ($\geq$20), and donor age ($\geq$55 years). Results of examination showed that overall percentage of the correct answers was significantly higher in exam 2013 than in exam 2012 (48.3% vs 32.7%; $P = .0001$). The survey after the simulation of multiorgan procurement revealed that most trainees thought that the simulation was useful and should be continued.

Conclusion. The novel educational program could allow young surgeons to make precise assessments and perform the exact procedure in the multiorgan procurement.

ALTHOUGH the number of deceased donors slightly increased since 2010 when the organ transplantation law was revised, there is still a large mismatch between supply and demand of deceased donors in Japan. To maximize the organ utility, multiorgan procurement of 5 organs including heart, lung, liver, pancreas, and kidney from most donors has become routine. Multiorgan procurement, however, is not an easy procedure, and it requires

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special technique and training. Sufficient donors are not available to perform on-site training for young surgeons. To prepare for the demand of increasing numbers of deceased donors in future, it is necessary to establish an educational program to ensure safe and expert multiorgan procurement. Herein, we report the development of an educational program and its efficacy in training of the liver procurement.

MATERIALS AND METHODS

Development of e-learning and simulation using pigs for multiorgan procurement are our main goal to establish the educational program. E-learning contains three dimensional computer graphic (3DCG) animations of the multiorgan procurement, explanation of both donor criteria and procurement procedure, and self-assessment examination.

It is crucial to elucidate the standard criteria for exact assessment of donors. From 1999 to 2013, 185 cases of donor procurement were performed, of which 160 cases of liver grafts were used for transplantation. The 25 risk factors of donors were analyzed in 138 adult cases of liver transplantation. The donor factors included date of procurement, hospital of procurement, admission date, age, sex, height, weight, body mass index, cause of death, length of hospital stay, length of cardiopulmonary resuscitation (>10 minutes), history of smoking, history of drinking, hemoglobin A1c, serum Na, serum blood urea nitrogen, serum creatinine, serum glucose, serum total bilirubin, serum aspartate aminotransferase, serum alanine aminotransferase, serum amylase, serum C-reactive protein, usage of high-dose dopamine (>15 mcg/kg/min), and usage of more than 2 vasopressors (from dopamine, dobutamine, noradrenalin, adrenalin, and vasopressin).

The 3DCG animation has been produced for liver and liver-pancreas procurement along with the scenario by Waseda University and Quality Experience Design Ltd, Tokyo. The solitary liver procurement procedure contained 2 sections: section A consisted of 11 sequences from opening the abdomen to cross-clamping the aorta, and section B consisted of 5 sequences from dissection of the common bile duct to procurement of the liver graft. The combined liver and pancreas procurement also contained 2 sections: section A (same as solitary liver procurement) and section C, which consisted of 10 sequences from mobilization of the duodenum to separation of liver from pancreas on the back table. The e-learning system was prepared to include 3DCG animations and explanation of both donor criteria and procurement procedure to educate a trainee prior to the simulation. This system will be open on the website for easy access to the trainees all across Japan.

Simulation for multiorgan procurement including heart, lung, liver, and pancreas was performed by each organ team in the Medical Innovation Institute of Technology Center, Johnson and Johnson, Inc. Japan (Sukagawa, Fukushima Prefecture, Japan) on August 10, 2013. The lectures for the procurement of each organ team were performed. The 3DCG animation was used for the liver procurement lecture. After that the self-assessment examination was performed.

A total of 41 trainees for liver procurement took the examination. The examination contained 7 questions related to both donor criteria and procurement of the liver; 4 questions (questions 1, 2, 5, 7) for complication asked the correct response to the donor status or complications during procurement procedure and 3 (questions 3,

Table 1. Contents of the Questions in Self-assessment Examination and Comparison of the Correct Answers Between Examinations in 2012 and in 2013

No.	QC	Questions	Answer Categories	Percentage of Correct Answers		*P*
				Exam 2012	Exam 2013	
1a	C	How would you respond when the blood pressure of the	Diagnosis	7.5	14.6	.259
1b		donor drops to 80/50 mm Hg under the dopamine drip at 5 μg/kg/min prior to the donor surgery?	Treatment	35.8	100.0	.0001
2a	C	How would you respond when you find a 3-cm diameter	Diagnosis	69.8	62.2	.215
2b		tumor on the surface of the liver during the donor surgery?	Treatment	22.6	24.4	.916
3a	A	How would you respond when you find the variant right	Procurement method	58.5	51.2	.314
3b		hepatic artery (the right hepatic artery from the superior mesenteric artery) under the circumstance that both liver and pancreas are planned to be procured?	Reconstruction method	32.1	61.0	.014
4a	A	How would you respond when you find the variant left	Procurement method	39.6	22.0	.023
4b		branch (the left hepatic artery from the left gastric artery) under the circumstance that both liver and pancreas are planned to be procured?	Reconstruction method	9.4	29.3	.022
5a	C	How would you respond when you get bleeding behind	Diagnosis	47.2	85.4	.0001
5b		the aorta during dissecting the abdominal aorta just above the bifurcation for cannulation?	Treatment	47.2	81.7	.002
6a	A	How would you respond when you find the variant renal	Place of cannulation	37.5	46.3	.644
6b		artery arising just above the aortic bifurcation during dissecting the abdominal aorta for cannulation?	Method of perfusion	12.5	19.5	.536
7a	C	How would you respond when you get bleeding behind	Method of hemostasis	27.5	31.7	.318
7b		the infraphrenic aorta during dissecting the aorta for cross-clamping?	Next step	40.0	48.8	.647
Total				34.8	48.4	.001

Abbreviations: QC, question category; C, complication; A, anatomy.

4, 6) for anatomy asked the correct response when you find an anatomical variation during procurement (Table 1). The result of the examination (exam 2013) was compared with the results after the lecture in 2012 (exam 2012) without using animation.

After demonstration of multiorgan procurement by the expert surgeons, the simulation for multiorgan procurement was performed by 97 trainees divided into 9 teams (each team consisted of approximately 10 young surgeons including 3 or 4 liver surgeons). After that, the survey was conducted.

Statistical analyses were performed with software SPSS version 21 (Japan IBM, Tokyo); univariate analysis with Fisher exact test and multivariate analysis with logistic regression analysis were used for risk factor analysis of donors, and t test was used for comparing examination results. P values less than .05 were considered statistically significant.

RESULTS

From the results from 138 cases of deceased donor liver transplantation in adults, 3 factors were independent for 3-month survival; cold ischemia time more than 10 hours (Exp (B) 61.3 (6.8–550.4), $P = .001$), Model for End-stage Liver Disease (MELD) score more than 20 (Exp (B) 4.9 (1.0–23.3), $P = .013$), and donor age more than 55 years (Exp (B) 6.0 (1.5–25.0), $P = .045$).

The results of the examinations showed that overall percentage of correct answers was significantly higher in exam 2013 than in exam 2012 (48.3% vs 32.7%; $P = .0001$; Table 1). While percentage of correct answers to the questions for complication was significantly higher in exam 2013 than in exam 2012 (54.5% vs 35.2%; $P = .0001$), there was no difference between exam 2013 and exam 2012 (36.0% vs 30.0%; $P = .271$) in percentage of the correct answers to the questions for anatomy.

Survey results from the 79 participants of the simulation of multiorgan procurement on August 10, 2013, showed participants in postgraduate 10 to 15 years were most predominant (37%), 52% of the participants could be operators in the any parts of the simulation, 94% agreed that the simulation was useful to improve their skills for procurement, 82% thought that they were prepared for real multiorgan procurement, 90% thought that they learned how to cooperate with other teams, and 99% thought that the simulation should be continued.

DISCUSSION

Three independent factors including cold ischemia time, MELD score, and donor age affected the early outcome in liver transplantation. Those were similar results compared to the one from earlier series of deceased donors [1]. Eliminating the recipients with high MELD score and elder donors is not practical. Minimizing cold ischemia time is the most certain and important method to improve early outcome. Close cooperation of the donor and recipient operations is critical to minimize cold ischemia time.

The results of the examination in 2013 improved significantly, compared to those in 2012, especially with the questions for complications. The 3DCG animation was used in the lecture prior to the simulation for the first time. The lecture with step-by-step explanation along with the animation and enriched contents of tips and pitfalls following each sequence of the animation can possibly be attributed to the improvement in the questions for complications in the 2013 examination. Instead, the explanation of anatomical variation was not sufficient because the animation was based on the regular anatomy in the limited time of the lecture. The e-learning has been prepared for the website and will be able to contain the enriched explanation for both complications and anatomical variations. A trainee could have enough time to study through e-learning and take the self-assessment examination prior to the simulation.

As apparent in the survey result, the simulation is one of the most important steps in the educational program to judge the self-assessment of surgical procedure as well as to learn how to cooperate with each other in multiorgan procurement. The survey results showed most of the participants thought that the simulation was useful. Financial support is the critical issue to continue the simulation. Either the government or hospitals registered for deceased donor transplantation should offer the sufficient support to maintain the quality of organ procurement in Japan.

In conclusion, the novel educational program could allow young surgeons to make precise assessment and perform the multiorgan procurement procedure. The establishment of this program could achieve safer donor operation, less graft failure, and better outcome of organ transplantation.

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ELSEVIER

Impact of Machine Perfusion Preservation of Liver Grafts From Donation After Cardiac Death

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ABSTRACT

Because of the critical shortage of deceased donor grafts, using a donation after cardiac death (DCD) donor is an important resource. However, the ischemic damage of those DCD grafts jeopardizes organ viability during cold storage. Maintaining organ viability after donation until transplantation is important for optimal graft function and survival. This review describes the effective preservation in transplantation for DCD livers. Concepts and development of machine perfusion for DCD liver grafts to reduce ischemia/reperfusion injury are discussed. Despite the fact that hypothermic machine perfusion might be superior to static cold preservation, DCD livers are exposed to hypothermia-induced damage. Recently, some groups introduced the beneficial effects of normothermic or subnormothermic machine perfusion in DCD liver preservation and transplantation.

THE SHORTAGE of donors for transplantation is a universal problem. The wait list for organs has continued to grow. However, the use of marginal donors is a promising way to increase the supply. In particular, use of organs from non–heart-beating donors (NHBD) and donation after cardiac death (DCD) are gaining importance as potential sources of vital organs for clinical transplantation. The two approaches to preservation before transplantation are simple cold storage (SCS) and machine perfusion (MP). The simplicity, lower cost, and need for transport make cold storage the method of choice for the majority of transplantation centers. However, the major principle of simple hypothermic liver preservation is the reduction of metabolic activity. Although MP using hypothermia may have a theoretical advantage in providing metabolic support and oxygenation, its use has not become widespread in clinical practice. Recently, the short- and long-term function of kidneys procured from DCDs by means of normothermic recirculation were reported [1]. The principle of normothermic and subnormothermic perfusion is to recreate the physiological environment by providing the essential substrates for cellular metabolism, oxygenation, and nutrition. In this review, based on the historical background of transplantation from DCD, clinical donor criteria for DCD livers and the progress of MP for DCD livers in cold storage are introduced. Finally, the method of rewarming preservation for DCD liver transplantation is introduced as a challenge using a new MP system.

HISTORICAL BACKGROUND FOR LIVER TRANSPLANTATION FROM DCD DONORS

In March 1995, an international workshop for NHBD was held in Maastricht, Netherlands. DCDs had been classified as the Maastricht classification [2]. Categories 1, 2, and 4 include uncontrolled DCDs, and category 3 includes controlled DCDs. DCDs have come to represent the fastest growing proportion of the donor pool. In some United Network for Organ Sharing (UNOS) regions with limited standard criteria for donors, DCDs comprised up to 16% to 21% of the total donor pool [3]. After successful use of DCD kidney grafts for clinical transplantation, interest has moved toward using extrarenal organs such as the liver, pancreas, and lungs [4]. However, in the early phase, liver transplantations from DCDs did not always show favorable post-transplantation results. The development of ischemic biliary stricture is a major source of morbidity after DCD liver transplantation.

Retransplantation is also associated with a significantly higher mortality risk. The difficulty with using DCD livers has been considered to be that, although the incidence of

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delayed graft function (DGF) in the kidneys is high, it can be treated with hemodialysis until the kidneys recover. In contrast, DGF in the liver often requires retransplantation as rescue therapy. For this reason, there has been great caution in using DCD liver grafts. Recently, the incidences of primary non-function (PNF) and severe DGF have been remarkably reduced due to the use of selected controlled DCD livers, better selection criteria for advanced preservation technologies, and shortened warm and cold ischemic times. However, this strategy does not always lead to a significant increase in donor numbers. Further studies are needed to identify clinical strategies, such as improving organ preservation, and policies to reduce incidences and improve the outcome of PNF and ischemic cholangiopathy in recipients who have DCD liver grafts.

MP Preservation of Liver Grafts

The introduction of kidney perfusion preservation in clinical practice started in the late 1960s. Folkert O.Belzer had already been working on the continuous hypothermic isolated perfusion and auto-kidney transplantation with blood [5] and cryoprecipitated plasma [6]. The hypothermic MP (HMP) of the first human kidney became a clinical reality soon thereafter; a patient received a kidney that had been preserved for 17 hours using this preservation circuit, and had acceptable function post-transplantation [6]. In the 1970s, HMP was used by transplantation centers mainly in the United States and Europe to preserve and transport kidneys. Consequently, different perfusion machines were also developed and used clinically for kidney preservation. Currently, there are three commercially available renal perfusion devices: the RM3 from Waters Medical Systems (Rochester, MN, USA) (Fig 1A), the LifePort from Organ Recovery Systems (Fig 1B), and the Kidney Assist by Organ Assist b.v. (Groningen, The Netherlands) (Figs 1C,D). However, in 1980, the development of the University of Wisconsin (UW) solution produced by the same UW group allowed surgeons to preserve kidneys for much longer time, up to 72 hours, by simple cold storage [7]. The development of the UW solution provided an alternative to MP, and most centers abandoned the clinical use of MP. During the last few decades, the success of kidney transplantation as the treatment of choice for end-stage renal failure has led to an increasing shortage of suitable organs. This shortage has forced the transplantation community to (re-) consider the transplantation of organs from marginal donors, such as older donors, hemodynamically unstable donors, and NHBD donors. Thereafter, the MP of kidneys from these marginal donors regained worldwide interest.

The international multicenter trial for HMP during kidney transplantation is a well-designed prospective randomized trial of paired kidneys [8], one preserved with SCS and one with MP. The study examined 672 renal transplantations performed in Europe. MP significantly reduced the risk of DGF, as well as significantly improving the rate of the decrease in the serum creatinine level. The number of use of HMP before kidney transplantation is now increased. Regarding liver preservation, Guarrera et al [9] showed the

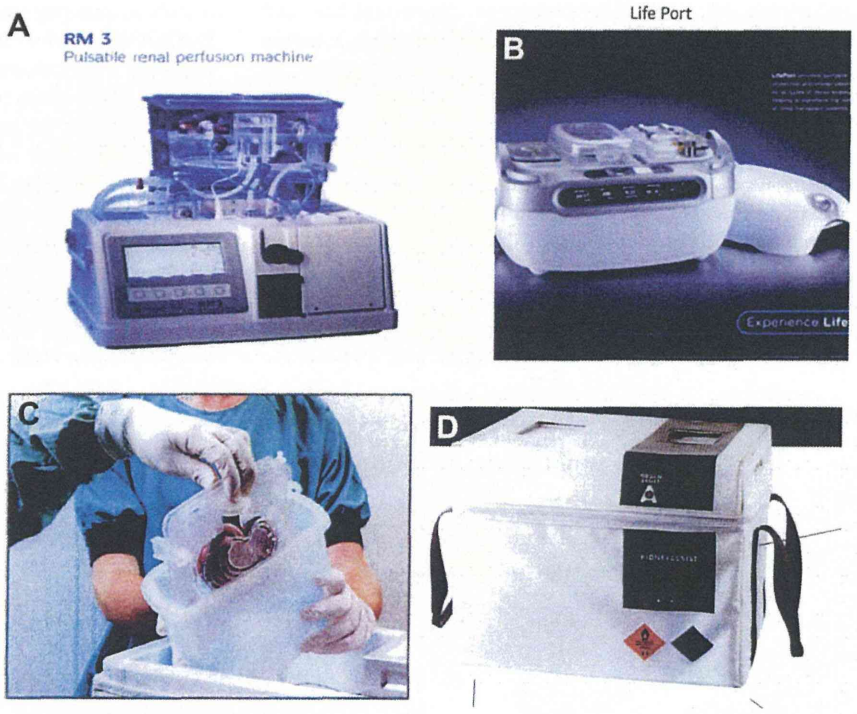

Fig 1. **(A)** RM-3 by Waters Medical System (Rochester, MN, USA). **(B)** LifePort Kidney Transporter by Organ Recovery System Des Plaines. **(C, D)** Kidney Assist by Organ Assist b.v. (Groningen, The Netherlands).

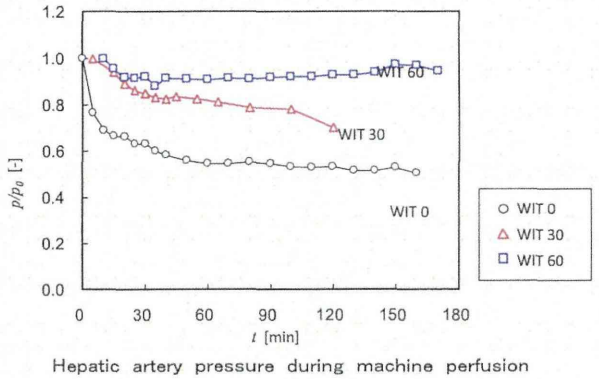

Fig 2. Changes of pressure in hepatic artery during machine perfusion.

outcomes of liver transplantation after 12 hours of HMP or with SCS in a miniature swine model using a new preservation solution, the Vasosolution, which uses a modified Belzer's MP solution. The serum aspartate aminotransferase (AST) and total bilirubin levels were similar in the HMP and SCS groups, indicating that HMP can be used successfully. Later, the Guarrera group reported successful use in human livers. The outcomes of liver transplantation were reported to be satisfactory compared with simple cold storage [10].

Pretransplantation viability testing for a DCD graft is particularly important. An advantage of using MP preservation is that it enables the performance of viability tests on the grafts while they are stored. Preservation by machine enables the physician to judge the acceptability of the graft by registering the flow and pressure characteristics and analyzing the enzymes in the perfusate. Developing a system of MP to establish viability assessments of the liver has not been easy due to the unique blood supply of liver grafts. Predicting viability by evaluating flow in the portal system is not possible because the portal flow is wide ranged and the systems used have found it difficult to generate portal pressure that shows efficient portal flow in the hypothermic stage. Even tissue and vascular resistance, which provide important information in kidney preservation, are particularly low due to easy destruction in the liver. The effluent AST and lactate dehydrogenase (LDH) levels collected in preservation solution have been reported to be useful and predictable biomarkers in previous reports [11–13]. Recently, Obara et al developed a novel liver perfusion system and found that the degree of decreasing hepatic arterial pressure is significantly correlated with the length of warm ischemic time (Fig 2) and the levels of liver enzymes (AST, LDH) in cold perfusate during continuous preservation [14] (Fig 2).

Challenge in DCD Liver Grafts Using MP

Despite successful MP for DCD kidney grafts, DCD liver transplantation has been challenging. There are important limitations of basic research using small animals because of the difficulties associated with assessment of the hepatic artery flow. In large-animal and clinical studies, successful transplantation was achieved by Brettschneider et al after 24 hours of MP in a canine model [15]. Starzl et al preserved the first 11 human livers up to 7.5 hours by the same method [16]. However, the use of fresh diluted blood is inconvenient in the clinical setting. Low-pressure HMP was applied via the hepatic artery in porcine livers for 2 hours before transplantation and compared to similar grafts stored in cold Euro-Collins solution for the same period. Both the LDH and AST levels were consistently lower in the HMP group compared with the SCS group [17]. A new preservation solution, Polysol, was developed for MP by the Amsterdam group in 2005. Polysol solution contains many vitamins and a protein-like, enriched tissue culture medium for functional recovery during preservation, which is expensive [18,19]. As for DCD liver grafts in large animals, most groups agree that 30 minutes of warm ischemic time (WIT) plus 4 to 5 hours of cold preservation results in primary loss of function in the pig liver [20,21]. Dutkowski used a large animal model to test whether short-term hypothermic oxygenated perfusion (HOPE) – treated DCD livers could experience the same benefits as those noted in the previous report using a rat model. The porcine DCD liver with 60 minutes of WIT preserved with SCS for 6 hours could be rescued by a 1 hour short-term HOPE treatment [22]. Lower values of AST and LDH after reperfusion, and a higher survival rate up to 30 hours in the HOPE group were shown. We developed a new preservation machine with a temperature-controlled system (NES) (Fig 3A). We reported beneficial functional recovery in the HMP group after 30 minutes of WIT plus 4

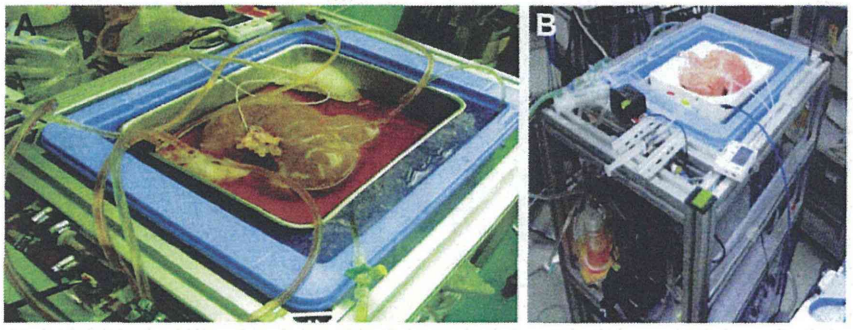

Fig 3. (A, B) Liver Perfusion System (NES).

to 5 hours of total ischemic time compared to the SCS-only group in a porcine liver transplantation model [23]. On the other hand, the concept for DCD graft has been changed and reported in recent years. Experimental studies have shown that even brief periods of cold preservation will cause injury to hepatocytes, Kupffer cells, and endothelial cells in DCD livers, even those later recirculated under normothermia. The use of normothermic extracorporeal membrane oxygenated (NECMO) perfusion is based on experimental studies which have shown that the recirculation of oxygenated blood at 37°C improves the cellular energy load, reduces tissue injury, and improves the post-transplantation graft function in livers damaged by the period of warm ischemia caused by cardiac arrest [24,25]. In 2002, the Hospital Clinic in Barcelona developed a clinical protocol to resuscitate organs from donors and to maintain viability for transplantation [26]. The protocol includes cannulation of the femoral vessels to establish an NECMO circuit. NECMO is used to reperfuse and oxygenate abdominal organs after cardiac arrest while the potential DCD is evaluated and consent for organ donation is obtained. In 2007, the first 10 human liver transplantations were performed with uncontrolled DCDs in which the donor was maintained with NECMO before organ retrieval. Ten DCD livers were transplanted with only 1 graft lost to PNF and 1 to hepatic artery thrombosis. In March 2013, two cases of human warm liver perfusion were successfully transplanted in Kings College Hospital group. The great advantage of normothermic preservation, including the use of NECMO, is the ability to overcome the disadvantaged aspects of hypothermic cellular physiology [27]. However, the use of blood-based perfusates may increase the risk of microvascular failure and sinusoidal plugging and bacterial growth. Normothermic preservation requires full metabolic support with a large machine. Additionally, any equipment failures result in unexpected warm ischemic injury. Therefore, achieving normothermic liver preservation remains troublesome and expensive. The reality of clinical organ retrieval might require a period of cold preservation due to transport between institutions. Some studies have investigated the perfusion temperature. For example, subnormothermic MP performed at 20°C resulted in reduced vasoconstriction, as well as lower metabolic requirements in DCD [28] and steatotic [29] rat models. Shigeta et al successfully transplanted porcine livers with 60 minutes of WIT plus 4 hours of total ischemic time by rewarming preservation from 4°C to 22°C using MP [30]. Development of liver perfusion system in the world is shown in Figure 4.

CONCLUSION

Traditional methods of hypothermic preservation based on both static and machine storage may not be best for DCD liver grafts because liver organs from DCDs have already suffered severe tissue damage secondary to hypoxia and hypoperfusion before the initial period of warm ischemia. Additional cold storage damage to the organ caused by hypothermic conditions may limit the ability to improve cellular function because metabolic activity is decreased in the cold storage. Ideally, these livers will be continuously perfused ex vivo with warm or subnormothermic oxygenated preservation solution. Rewarming preservation during perfusion may become practically available and useful.

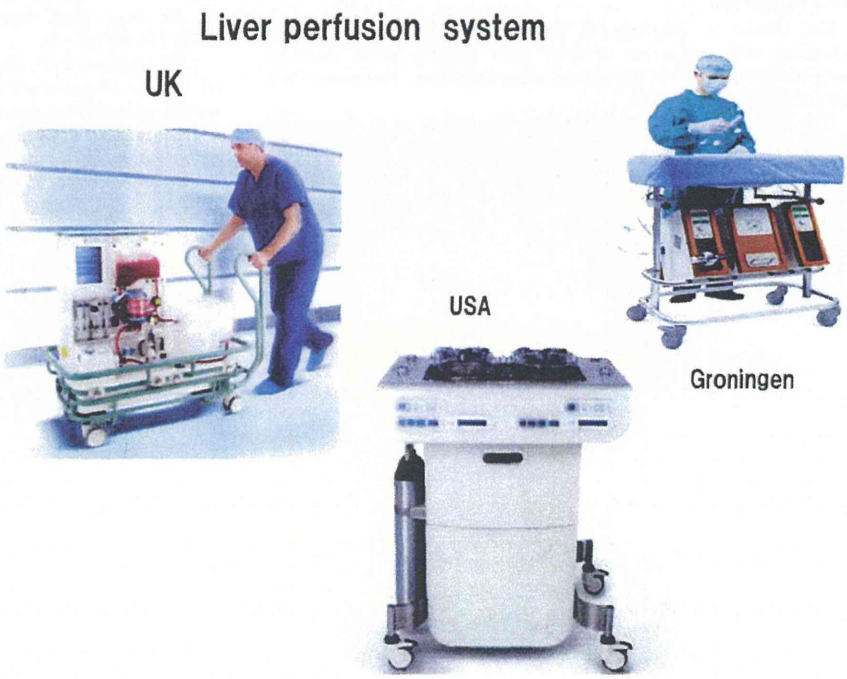

Fig 4. Development of liver perfusion system.

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EDITORIAL

Is low central venous pressure effective for postoperative care after liver transplantation?

Susumu Eguchi

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The central venous pressure (CVP) has been regarded as an important factor for reducing blood loss and the blood transfusion rate during major hepatectomy, and can be controlled by positive end-expiratory pressure (PEEP) or certain drugs and the optimal positioning of the patient [1–4].

In this issue of *Surgery Today*, Wang et al. [5] describe the beneficial effects of lowering the CVP for achieving a better postoperative outcome compared with conventional fluid management in deceased donor liver transplantation based on a prospective randomized controlled study. They report that the low CVP group showed (1) less intraoperative blood loss, (2) a decreased need for intraoperative blood transfusion, (3) fewer lung-related complications at 1 month postoperatively, (4) a shorter intubation period and (5) equal patient survival at 1 year after liver transplantation. A previous retrospective study showed intraoperative blood transfusion to be a risk factor for postoperative lung complications [6]. The present study was done in a prospective, randomized manner, which yielded the same results as those seen in the previous retrospective study. The methods used to reduce the CVP in the present study were the use of the Fowler position, fluid restriction and drugs (e.g., nitroglycerin, furosemide and somatostatin). These methods have also been used in previous studies to reduce the intraoperative CVP, and therefore they appear to be valid for this kind of study [2].

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Although the results provided in the article were of high importance, lowering the CVP during liver transplantation might still be controversial and may have ambivalent aspects with regard to the lack of a relationship between the early complication rates, including renal, hepatic and pulmonary complications, and the CVP following liver transplantation [7–10]. For example, apart from the reduced pulmonary complication rate, and the lower blood loss and blood transfusion rate, what would be the influence of lowering the CVP on the postoperative care following liver transplantation? If blood product administration during the intensive care period is increased, then the policy to limit CVP during surgery would be in vain. Therefore, the readers will also want to know: How would the perfusion in the organ be affected? How would the lactate level in the blood after LT be affected, not only at the end of surgery but also during the postoperative period? How would the post-transplant blood product requirements be affected?

In fact, the period in which the CVP is lowered may be of importance. For example, Feng et al. [7] reported that a low CVP during the pre-anhepatic phase reduced the intraoperative blood loss, protected the liver function and it also had no detrimental effects on the renal function after LT. On the other hand, Cywinski et al. reported that a low CVP during the post-anhepatic phase was not associated with any benefit in terms of immediate postoperative allograft function, graft survival or patient survival [10]. In addition, the cut-off value for CVP monitoring in previous studies varied between 5 and 10 mmHg.

We therefore await further reports from other investigators before drawing any definitive conclusions about the above-mentioned issues, since liver transplant surgery, especially partial liver transplantation, is often affected by multiple factors [11].

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LIVER TRANSPLANTATION 19:666, 2013

LETTER TO THE EDITORS

False Positivity for the Human Immunodeficiency Virus Antibody After Influenza Vaccination in a Living Donor for Liver Transplantation

Received February 13, 2013; accepted February 25, 2013.

TO THE EDITORS:

Because of increased productivity and availability, more people have had the chance to undergo prophylactic influenza vaccination. It has been reported that influenza vaccination has cross-reactivity with human immunodeficiency virus (HIV) antibody assays, but this information is not well known in the field of transplantation.[1] Recently, we experienced a case of living donor liver transplantation in which a healthy donor candidate was frightened and was further screened for the HIV antibody.

The patient was a 43-year-old female who was a candidate for partial liver donation for her husband, who was suffering from hepatocellular carcinoma associated with hepatitis B liver cirrhosis. She had never undergone a blood transfusion or abused drugs before her screening for living partial liver donation. According to her laboratory results, she was positive for the HIV antibody (1.7 cut off index). Otherwise, all data, including hepatitis B antibody results, were within normal limits. It was found that she had undergone vaccination for influenza 1 week before the screening. She was referred to a specialist in HIV infection, and western blotting for all antibodies (GP160, GP110/120, P68/66, P55, P52/51, GP41, P40, P34/31, P24/25, and P18/17) was negative. HIV RNA was undetectable in her blood (<40 copies/mL). Thus, she was considered to be HIV-negative with a high level of confidence and subsequently donated the left lobe of her liver. The recipient remained negative for the HIV antibody even after living donor liver transplantation.

With the prevalence of influenza vaccination and organ donation, physicians should keep in mind that recent inoculation with any brand of influenza vaccine is associated with a false-positive screening assay for HIV antibodies.[2]

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The protocol for our living donor liver transplantation received a priori approval by the institutional review committee.

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Hepatology Research

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Original Article

Disease recurrence plays a minor role as a cause for retransplantation after living-donor liver transplantation for primary biliary cirrhosis: A multicenter study in Japan

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Aim: To clarify the role of disease recurrence as a cause of graft loss after living-donor liver transplantation (LDLT) for primary biliary cirrhosis (PBC), we investigated explant grafts, as well as the native liver and liver biopsy specimens, of patients who underwent retransplantation.

Methods: Of 516 patients who underwent LDLT for PBC and were registered in the Japanese Liver Transplant Registry, nine patients (1.7%) underwent retransplantation.

Results: Seven patients undergoing retransplantation later than 6 months after primary liver transplantation (LT) were enrolled. All seven patients were female, with ages ranging from 34–57 years, and Model for End-Stage Liver Disease scores ranging 10–28. The right lobe was used as graft in one and the left lobe in six. The initial immunosuppression regimen was tacrolimus in six and cyclosporin in one. The period between the primary LT and retransplantation ranged 11–120 months, with a median of 36 months. Three patients survived and four patients died due to poor graft functions or complications after retransplantation. The primary causes of primary graft loss revealed by histological examination of the explant livers were chronic rejection in three, portal thrombus and/or steatohepatitis in three and outflow block in one. PBC recurrence was observed in 3 and the stage was mild in all.

Conclusion: PBC recurrence has a small impact as a cause of graft loss after LDLT.

Key words: histology, living-donor liver transplantation, primary biliary cirrhosis, recurrence, retransplantation

INTRODUCTION

PRIMARY BILIARY CIRRHOSIS (PBC) is a major indication for liver transplantation (LT). Because autoimmune mechanisms possibly contribute to the etiology of PBC, the possibility of recurrence after transplantation and the impact on the clinical course have been reason for considerable concern. Rates of recurrence have been reported to range 9–35% in deceased-donor LT in Western countries.[1] In living-donor liver transplantation (LDLT) in Japan, the rates have been reported to range 1–40% on the basis of histological evidence.[2–6] However, this range is not reliable because routine liver biopsy is not standard. Furthermore, the impact of recurrence on the clinical course is unclear. The proportion of grafts lost due to disease recurrence was reported to be 2% 10 years after transplantation by Rowe *et al.*[7] On the other hand, Charatcharoenwitthaya *et al.* reported that recurrent PBC was not associated

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with death or retransplantation.[8] There have been no reports of graft failure secondary to recurrent PBC in Japan, either.[2–6]

The difficulty of performing histological diagnosis of recurrent PBC using needle biopsy specimens is a barrier for studying the impact of recurrent PBC, although histological examination is the gold standard.[6,9,10] Heterogeneity of histological changes is a major hurdle for diagnosis on the basis of needle biopsy specimens. To overcome this problem, we conducted a multicenter study using whole hepatic grafts explanted during retransplantation for PBC.

METHODS

OF 516 PATIENTS who underwent LDLT for PBC and who were registered in the Japanese Liver Transplant Registry, nine patients (1.7%) underwent retransplantation. The demographic data of the recipients and primary donors and information on the clinical courses were obtained.

A current author (Y. N.) performed histological investigation of the native liver, the liver biopsy specimens if present, and the explant grafts. The diagnosis of acute cellular rejection (ACR) and chronic rejection was made according to the Banff criteria.[11,12] Staging of PBC was based on the Nakanuma staging system.[13]

This study was approved by the Ethical Committee of Tokyo Women's Medical University as the central office of the multicenter study, or at each institution if necessary, and it conforms to the provisions of the Declaration of Helsinki (as revised in Seoul, Korea, October 2008).

RESULTS

OF THE NINE patients who underwent retransplantation, two died within 6 months after retransplantation. One died due to graft failure secondary to severe acute rejection and another due to small-for-size syndrome. In both cases, we examined the clinical courses and explanted livers, and confirmed the diagnoses. We enrolled the remaining seven patients in this study.

The demographic and operative data of the recipients and primary donors and the clinical courses are shown in Table 1. All patients were female and had histories of pregnancies. Human leukocyte antigen DR8 was detected in all recipients except no. 5 and in the donors of recipients no. 3, 6 and 7. The donor was the patient's husband in two cases, son in three, sister in one and mother in one.

Primary immunosuppression was performed with a triple regimen consisting of calcineurin inhibitor, steroids and antimetabolites (azathioprine, mizoribine) in three patients, and calcineurin inhibitor and steroids in four patients. The calcineurin inhibitor was tacrolimus in all patients except no. 6 in which cyclosporin was converted to tacrolimus 1 year after transplantation.

All patients were treated with ursodeoxycholic acid (UDCA) and no. 1 and 7 with bezafibrate prior to primary transplantation. All patients were given UDCA after transplantation and only no. 3 was given bezafibrate transiently.

Patients 1, 4, 6 and 7 continued to complain of fatigue even after transplantation. Postoperative complications are shown in Table 1. The period between the primary transplantation and retransplantation ranged 11–120 months, with a median of 36 months. Three patients survived and four patients died due to poor graft functions or complications after retransplantation.

Histological findings of the native liver, the liver biopsy specimens and the explant grafts are summarized in Table 2. The stage of PBC of the native liver was 4 in all patients except no. 7. The primary causes of primary graft loss were chronic rejection in three (no. 2, 3 and 6), portal thrombus in one (no. 7), nonalcoholic steatohepatitis (NASH) in one (no. 4), portal thrombus and NASH in one (no. 5), and outflow block in one (no. 1). Briefly, submassive necrosis from ischemic etiology and liver cirrhosis of chronic congestive etiology were observed in no. 1. Foamy cell arteriopathy, duct loss with degenerative epithelial damage with severe cholestasis, and centrilobular and C-C and P-C bridging fibrosis were observed in no. 2. In both patients 4 and 5 with NASH, the stage had progressed from stage 2 in the biopsy specimens to stage 3 in the explanted livers.[14] Portal vein thromboembolism and altered intrahepatic circulation was also observed in no. 5. Marked centrilobular necrosis and hemorrhage with mild inflammation and fibrosis and portal venopathy with repeated thromboemboli were observed in no. 7.

Recurrence of PBC was observed in no. 2, 6 and 7 in the specimens of on-demand needle or wedge biopsies and confirmed in the explanted livers (Figs 1–3). Histological progression of PBC was very mild or mild and the recurrence was not the main cause of graft failure. We evaluated: (i) mononuclear inflammatory infiltrates; (ii) formation of lymphoid aggregates; (iii)

Table 1 Demographic data, operative data and clinical courses

Patient no.	1	2	3	4	5	6	7
Age (years)	52	40	34	37	47	47	57
Time from diagnosis to LT (months)	22	3	60	55	65	132	99
AMA	>320	80	40	80	NA	Negative	160
Anti-M2 (mg/dL)	1859	1550	NA	NA	NA	NA	152
IgM (mg/dL)	1037.8	172.8	426	115	340	NA	524
IgG (mg/dl)	1945.7	884.2	1774	1373	2921	NA	180
ANA	640	±	Negative	±	Negative	320	NA
Child–Pugh score	7	8	11	12	12	14	10
MELD score	10	11	17	24	22	28	11
Primary donor							
Relation	Husband	Mother	Husband	Sister	Son	Son	Son
Age (years)	50	60	34	47	19	20	23
Sex	Male	Female	Male	Female	Male	Male	Male
Operative variables							
Blood type combination	Compatible	Identical	Identical	Compatible	Compatible	Compatible	Identical
GRWR	1.00	0.95	0.88	0.77	1.07	0.58	0.90
Graft type	Left	Right	Left	Left	Left	Left	Left
Operation time (min)	751	550	665	615	730	680	870
Cold ischemic time (min)	82	38	56	53	111	95	131
Warm ischemic time (min)	53	44	33	40	38	45	41
Blood loss (g)	2400	2470	850	10 320	6190	8005	4500
Postoperative complications	Hemoperitoneum, biliary stenosis, ACR, hepatic vein stenosis	Biliary stenosis, ACR, EBV infection	Chronic rejection	ACR	ACR Artery-portal shunt	Biliary leakage and stenosis	Portal vein thrombosis
Time of retransplantation (months)	39	24	36	88	120	20	11
Outcome of retransplantation	Dead (49 days)	Alive	Dead (59 days)	Alive	Alive	Dead (15 days)	Dead (284 days)
Causes of death	Lung bleeding		Graft failure			Graft failure	Graft failure

ACR, acute cellular rejection; AMA, antimitochondrial antibody; ANA, antinuclear antibody; EBV, Epstein–Barr virus; GRWR, graft recipient weight ratio; Ig, immunoglobulin; LT, liver transplantation; MELD, Model of End-stage Liver Disease; NA, not applicable.