REVIEW

Liver Transplantation

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Liver transplantation has become a lifesaving procedure for patients who have chronic end-stage liver disease and acute liver failure. The satisfactory outcome of liver transplantation has led to insufficient supplies of deceased donor organs, particularly in East Asia. Hence, East Asian surgeons are concentrating on developing and performing living-donor liver transplantation (LDLT). This review article describes an update on the present status of liver transplantation, mainly in adults, and highlights some recent developments on indications for transplantation, patient selection, donor and recipient operation between LDLT and deceased-donor liver transplantation (DDLT), immunosuppression, and long-term management of liver transplant recipients. Currently, the same indication criteria that exist for DDLT are applied to LDLT, with technical refinements for LDLT. In highly experienced centers, LDLT for high-scoring (>30 points) Model of End-Stage Liver Disease (MELD) patients and acute-on-chronic liver-failure patients yields comparably good outcomes to DDLT, because timely liver transplantation with good-quality grafting is possible. With increasing numbers of liver transplantations and long-term survivors, specialized attention should be paid to complications that develop in the long term, such as chronic renal failure, hypertension, diabetes mellitus, dyslipidemia, obesity, bone or neurological complications, and development of de novo tumors, which are highly related to the immunosuppressive treatment. **(Gut and Liver 2009;3:145-165)**

Key Words: Liver transplantation; Deceased donor liver transplantation; Living donor liver transplantation

INTRODUCTION - HISTORICAL PERSPECTIVES

Today, liver transplantation is a lifesaving procedure for patients with chronic end-stage liver disease and acute liver failure (ALF) when there are no available medical and surgical treatment options.[1-3] Thomas Starzl performed the first three human liver transplantation at the University of Colorado in 1963, but did not achieve 1-year survival until 1967. Over the next 15 years, relatively few liver transplantation were performed, and the 1-year survival rate was only 30% until the late 1970s and early 1980s when the implementation of cyclosporine-based immunosuppression led to doubling of the 1-year survival rate.[1] In 1983, these improved outcomes led to the decision at a National Institutes of Health Consensus Development Conference that liver transplantation was no longer experimental procedure and deserved broader application in clinical practice.[4] This meeting initiated the modern era of liver transplantation and resulted in the propagation of liver transplantation across the United States and around the world.

Since the early 1980s, there have been significant advances in all aspects of liver transplantation, including recipient selection, donor management, operation technique, immunosuppression, and postoperative management of liver recipients. These changes, which have marked the evolution from an experimental technique to established and routine therapy, have resulted in enormous improvements in outcome. The overall 1-year survival for adult and pediatric deceased donor liver transplantation (DDLT) is now expected to be in excess of 85%, with 5- and 10-year survival in excess of 70% and 60%, respectively.[5-8]

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The success of liver transplantation as treatment for most types of acute and chronic liver failure has led to increased referrals for transplantation in the setting of a relatively fixed supply of cadaveric donor organs.[1] At the end of 2006, more than 17,000 patients were listed for liver transplantation in the United States.[9] Despite performance of more than 6,000 liver transplantations annually in the United States during the past several years,[9,10] only one thirds of candidates received liver transplantation and almost 2,000 deaths have occurred annually in patients listed for liver transplantation during past 6 years.[1] The persistent shortage of donor organs is ob-

viously insufficient to meet the growing demand for liver transplantation. This kind of imbalance between the supply of donor organ and the patients' numbers demanding liver transplantation is extremely severe in the region of East Asia including Korea, Japan, Hong Kong and Taiwan (Fig. 1). The disparity between supply and demand might be related to inadequate understanding for organ donation after brain death mainly influenced by Confucianism and also insufficient legal supporting system. Although the first successful living donor liver transplantation (LDLT) was performed for pediatric recipient using lateral sector (Couinaud's segment 2 and 3) by Strong RW in 1989, the above situation in the East Asia led surgeons having humanistic enthusiasm to concentrate on developing and performing LDLT as an alternative.

The first successful liver transplantation in Korea was performed using deceased donor whole-size liver by Kim ST in 1988.[11] In the early 1990s, liver transplantation was slowly developed as a feasible option in the treatment of end-stage liver disease in Korea mainly because of the severe shortage of deceased donor liver grafts. In 1994, Lee SG performed the first successful pediatric LDLT in 6-month old female biliary atresia child with her father's left lateral sector.[12]

The success in pediatric liver transplantation and the shortage of organs provided the necessary incentive to attempt living donations for adult recipients.[13] The accumulated knowledge of the sophisticated hepatobiliary surgery as well as the experiences of DDLT and pediatric LDLT finally made us to perform the first successful adult LDLT using left lobe in 1997 February.[14] The emerging awareness of the importance of graft volume and low graft-to-
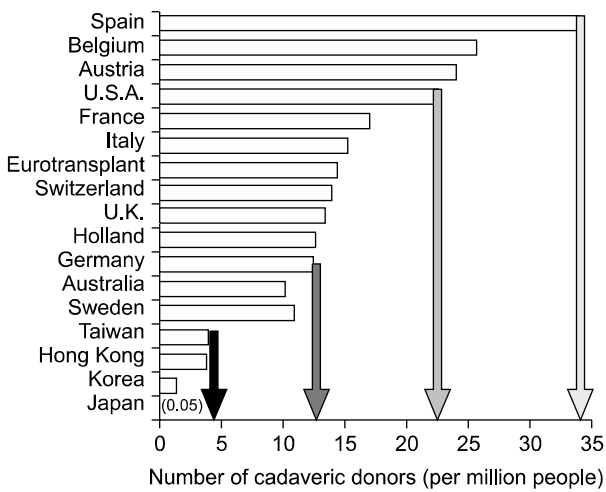

Fig. 1. Number of deceased donor livers available in various countries in 2000. Reprinted from de Villa VH, Lo CM, Chen CL. Ethics and rationale of living-donor liver transplantation in Asia. Transplantation 2003;75(3 Suppl):S2-S5.
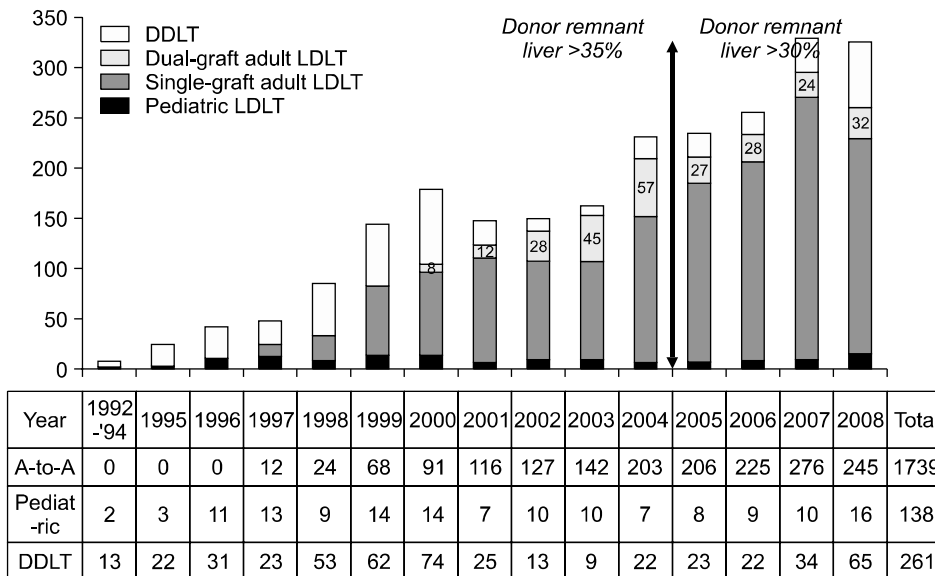

Fig. 2. Annual number of liver transplantations performed at the Asan Medical Center, Ulsan University College of Medicine. The reduction in the accepted remnant liver volume from > 35% to >30% of the donor's total liver volume in 2005 resulted in a decrease in the proportion of dual-graft LDLTs. In 2008 there was a marked increase in organ donations, which was fueled by organ donation from a famous boxer in early 2008, hence reducing the number of LDLTs.

LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation.

Year	1992-'94	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	Total
A-to-A	0	0	0	12	24	68	91	116	127	142	203	206	225	276	245	1739
Pediatric	2	3	11	13	9	14	14	7	10	10	7	8	9	10	16	138
DDLT	13	22	31	23	53	62	74	25	13	9	22	23	22	34	65	261

recipient weight ratio led us to initiate right lobe LDLT in adults from 1997 July.[13] On the contrary to Hong Kong Group,[15] we designed modified right lobe graft to reduce the risk to the donor after right lobe donation by leaving middle hepatic vein to the donor's remaining liver, and reconstruction of divided but sizable-middle hepatic vein branches to prevent congestion of anterior sector in the recipient's side.[16,17] This innovative design of right lobe graft has contributed to rapid expansion of our adult living donor liver transplantation program (Fig. 2). In addition, in order to alleviate the small for size graft problem to the recipients and donor risk from harvesting right lobe from suboptimal donor simultaneously, dual-grafts LDLT was initiated in 2000 March.[18] Thereafter, the donor rejection rate due to inadequate volume or excessive steatosis was reduced from 40% to 20%.[19]

The aim of this review is to give an update on the present status of liver transplantation mainly in adults, and to highlight some recent developments on indications for transplantation, patient selection, perioperative care, immunosuppression, and long-term management of liver transplant recipients.

INDICATIONS AND CONTRAINDICATIONS

Cirrhosis accounts for more than 80% of transplants performed in adults, and the most important indications for liver transplantation in the United States are hepatitis C (21%), alcoholic liver disease (16%), cholestatic liver disease including primary biliary cirrhosis and sclerosing cholangitis (17%). Other indications are chronic hepatitis (hepatitis B, autoimmune hepatitis), metabolic disease (Wilson's disease, nonalcoholic steatohepatitis), fulminant hepatic failure, and non-metastatic hepatocellular carcinoma (HCC).[20] However, the most common indications of liver transplantation in Korea are hepatitis B (81%) including HCC (21.5%) and then fulminant hepatic failure (7%), alcoholic liver disease (4%) and hepatitis C (3%). Recently the proportion of hepatitis C and alcoholic liver disease is slowly increasing and the indications of liver transplantation become resembling to Western countries year by year (Fig. 3).[21] Major pediatric indications for liver transplantation include biliary atresia and metabolic diseases.

Patients with hepatitis B cirrhosis and high viremia were not eligible for transplantation in the past because of the high risk of recurrence after transplantation with consequent rapid graft loss. Since the availability of antiviral medication, high viremia is treatable and transplantation has become a more realistic option with excellent graft and patient survival that is even superior to that of many other indications.[22] After transplantation, antiviral treatment, often including hepatitis B immune globulin, is continued to prevent recurrent infection.[23]

HCC is a well-recognized indication for transplantation when the patients have Child B and C liver cirrhosis at
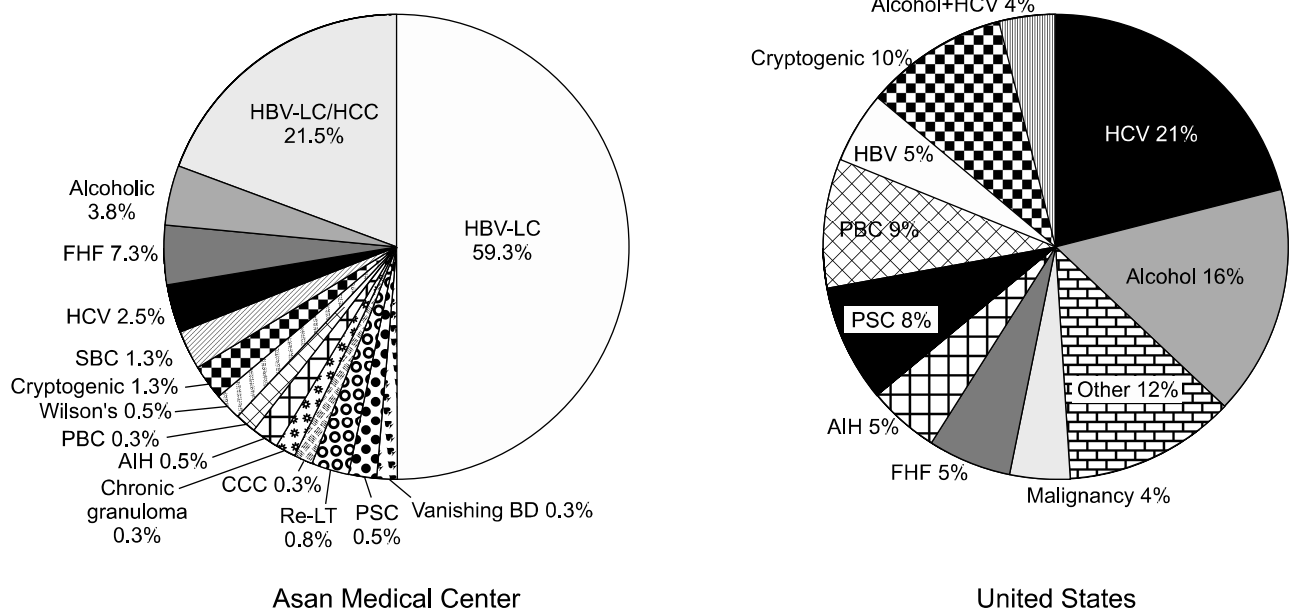
Fig. 3. Comparison of indications for liver transplantation between Korea and the United States.
HBV, hepatitis B virus; LC, liver cirrhosis; HCC, hepatocellular carcinoma; FHF, fulminant hepatic failure; HCV, hepatitis C virus; SBC, secondary biliary cirrhosis; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; CCC, cholangiocarcinoma; Re-LT, retransplantation; PSC, primary sclerosing cholangitis; BD, bile duct.

the same time. Generally, only patients who meet the Milan criteria of a single tumor up to 5 cm or up to three tumors with less than 3 cm and no major vascular invasion such as portal and hepatic vein, as determined by imaging studies,[24] are approved by the transplant organizations in most countries. Survival rates for these patients are comparable to those for cirrhosis leading to transplant without a complicating HCC recurrence. Preoperative base-line metastatic work-up includes bone scan and chest computed tomography (CT). Recently, positron emission tomography (PET) scan also tends to be included because of the usefulness to find undetected malignancy and to avoid legal issue. Discussion at present focuses on expansion of these strict criteria, as on the one hand the removed liver often shows more tumor lesions than expected, and on the other hand patients with somewhat larger lesions often do well.[25] Yao *et al.* have shown that patients who have single tumor 6.5 cm in diameter or smaller or three or fewer tumors with largest being 4.5 cm or less in diameter and a total tumor burden of 8.0 cm or less (the so-called "UCSF criteria") achieved results that were not different from those of patients belonging to Milan criteria.[26] Lee *et al.* proposed Asan Medical Center (AMC) criteria from the results of LDLT for HCC, based on explant pathology, that were largest tumor diameter ≤5 cm, number ≤6, and no gross vascular invasion. It had similar prognostic power but highest discriminatory power than Milan and UCSF criteria.[27] Finally, radiofrequency ablation and chemoembolization have become bridging therapies to transplantation while patient is waiting on the liver transplant list.[28,29]

Chronic hepatitis C virus (HCV) infection is the leading indication for liver transplantation in United States, and the number of transplantation for this indication is expected to increase dramatically over the next 10 to 20 years.[30,31] Retransplantation for patients who develop allograft dysfunction as a result of recurrent hepatitis C remains controversial, because outcomes are often poor,[32] and antiviral therapy of recurrent HCV infection has relatively low efficacy.[33]

For alcoholic liver disease, the prerequisites for transplantation in most centers are alcohol abstinence for at least six months and active treatment for alcohol dependency before transplantation.[34,35]

ALF, also called "fulminant hepatic failure," and the more indolent variant, subfulminant hepatic failure, are characterized by the development of liver failure manifested by coagulopathy, jaundice, and encephalopathy leading to coma in the absence of chronic liver disease.[36] ALF accounts for 5% to 6% of all liver transplantations.[9] Acetaminophen hepatotoxicity is the leading cause of

ALF, whereas idiosyncratic drug-induced liver injury is the major cause of subfulminant hepatic failure.[36] Patients who have ALF can recover spontaneously, but those with subfulminant hepatic failure are expected to have 100% mortality without transplantation.[10,36] Transplantation indications ALF are usually based on King's College criteria,[37] and/or Clichy criteria.[38] However, it is often recommended that patients with ALF who fail to meet King's College criteria still be considered for liver transplantation, because spontaneous recovery is not guaranteed.[1] Timely referral and liver transplantation is of paramount importance, because death from sepsis and cerebral edema may occur within days of onset of stage 3 or 4 hepatic encephalopathy.[2,10,36] Lee *et al.*[39] described that the timely LDLT using appropriate graft type sufficing at least more than 40% of patient's standard liver volume with minimal steatosis resulted in remarkably improved survival rate for adult ALF patients in this region where deceased organ donation is very scarce.

Graft failure with the need for retransplantation accounts for an increasing number of transplantations. Shortly after transplantation, this mainly concerns primary nonfunction of liver grafts and hepatic artery thrombosis, later biliary complications and recurrent hepatitis C can become indications for retransplantation.[25]

In general, the past few years are characterized by an increasingly shorter list of absolute contraindications and a growing list of indications for liver transplantation. Specific type of Budd-Chiari syndrome and severe portal vein thrombosis and/or stenosis, previously considered as a anatomic abnormality precluding liver transplantation, were no longer contraindication for liver transplantation. For Budd-Chiari syndrome, thrombosis and/or stenosis extending to intrapericardial inferior vena cava (IVC) and almost orifice of right atrium, Lee *et al.* replaced the diseased stenotic retrohepatic vena cava of the recipient with a large caliber Dacron interposition graft between right atrium and infraheaptic IVC (Fig. 4).[13] Portal venous thrombosis, sclerosis and size discrepancy between the graft and recipient's portal vein (PV) are other issues that make it difficult or impossible to perform standard end-to-end anastomosis. These problems are usually overcome by the use of PV thrombectomy and venoplasty, and additionally portal vein stenting by using intraoperative portogram if necessary (Fig. 5).[40] Sometimes interposition vascular graft from superior mesenteric vein or left renal vein when large splenorenal shunt is accompanied, should be used to supply mesenteric blood to the graft, which is essential for graft regeneration (Fig. 6).[41,42]

Most generally accepted absolute contraindications to transplantation are noted in Table 1. Transplant centers
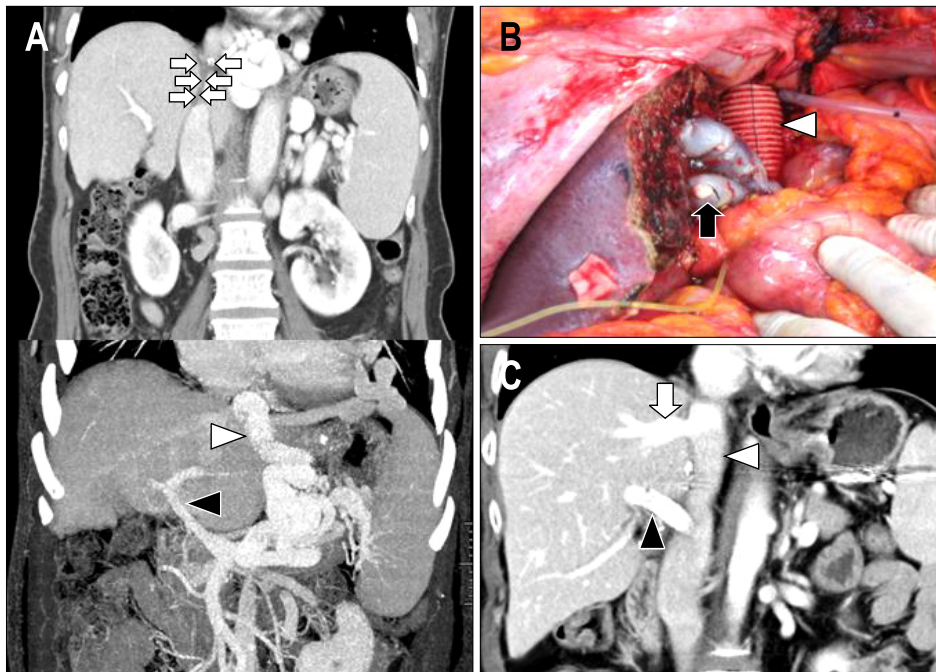
Fig. 4. LDLT with replacement of the inferior vena cava using a Dacron interposition graft for Budd-Chiari syndrome. (A) Preoperative CT scan showing typical findings of Budd-Chiari syndrome: retrohepatic obliteration of the inferior vena cava (multiple arrows), and portal vein stenosis and a large coronary collateral vein (black and white arrowheads, respectively). (B) Intraoperative photograph showing replacement of the inferior vena cava with a Dacron interposition graft between the right atrium and the suprarenal inferior vena cava (white arrowhead), and middle hepatic vein tributaries reconstructed using cryopreserved cadaveric iliac vein grafts. (C) Two-year postoperative CT scan revealing a patent replaced inferior vena cava, right hepatic vein, and portal vein without stenosis (white arrowhead, white arrow, and black arrowhead, respectively).
LDLT, living donor liver transplantation.
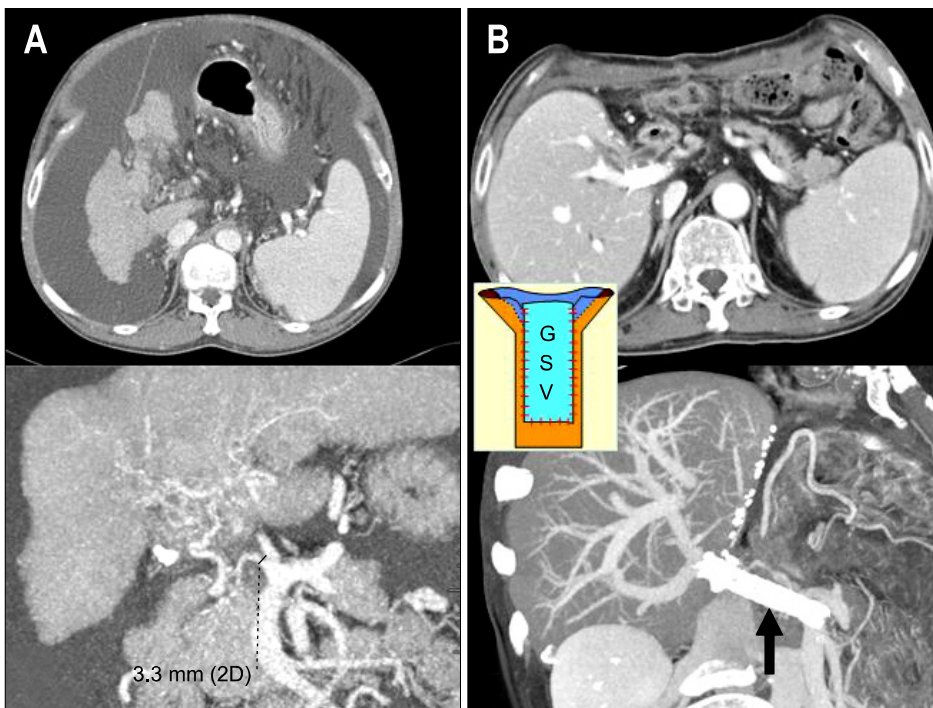
Fig. 5. Portal vein plasty with the great saphenous vein and intraoperative stent placement for severe portal vein stenosis. (A) Preoperative CT scan showing severe portal vein stenosis and abundant ascites. (B) The liver graft regenerated well and ascites had disappeared by the 2-month postoperative follow-up, as revealed by this CT scan, after intraoperative portal vein plasty with an autogenous great saphenous vein (GSV, indicated by the separate figure in the small box) and additional stent placement (black arrow).
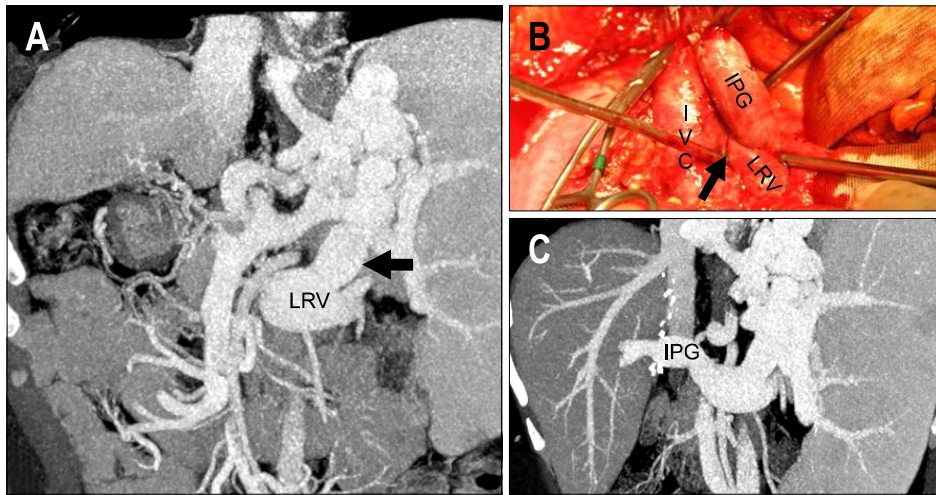
Fig. 6. Renoportal anastomosis using a cadaveric fresh iliac vein graft for an obliterated portal vein, and large spontaneous splenorenal shunts. (A) Preoperative CT scan showing obliterated portal vein stenosis and large spontaneous splenorenal shunts draining most of the splanchnic blood flow into the left renal vein (LRV, black arrow). (B) Intraoperative photography showing an interposition cadaveric fresh iliac vein graft (IPG) anastomosed to the left renal vein. The black arrow indicates the interruption suture running between the inferior vena cava (IVC) and the left renal vein in order to prevent portal flow stealing. (C) Patent interposition iliac vein graft between the left renal vein and the grafted portal vein. A well-regenerated liver is visible on the 2-year postoperative follow-up CT scan.

Table 1. Contraindications to Liver Transplantation

Anatomic abnormality precluding liver transplantation
Malignancy outside the liver
Untreated sepsis
Advanced cardiopulmonary disease
Active alcohol and drug use
AIDS

are now increasingly offering liver transplantation to carefully selected older patients and human immune-deficiency virus (HIV)-infected individuals in the absence of acquired immune deficiency syndrome (AIDS).[43]

LISTING AND TIMING OF LIVER TRANSPLANTATION

The presence of cirrhosis alone is not sufficient to warrant transplantation. Although the high level of morbidity and mortality in chronic liver disease is related to complications of cirrhosis, the well-compensated cirrhotic patient can remain stable for many years. Fattovich et al.[44] reported a 91% 5-year survival rate in a cohort of 384 cirrhotic HCV patients. However, once an index manifestation of decompensation had occurred such as variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and occurrence of HCC, etc., survival dropped to 50% at 5 years, suggesting that referral for liver transplantation should be considered once an index

Table 2. Model for End-Stage Liver Disease Score

MELD score	Three-month mortality (Hospitalized patients)
≤9	4%
10-19	27%
20-29	76%
30-39	83%
≥40	100%

MELD score=$9.57 \times \log_e$ (Creatinine mg/dl)+$3.78 \times \log_e$ (Bilirubin mg/dl)+$11.20 \times \log_e$ (INR)+6.43

Reprinted from Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-470.

complication has occurred.

Since the application of the Model of End-Stage Liver Disease (MELD) score for organ allocation in 2002 by the Unite Network for Organ Sharing (UNOS), cirrhotic patient has to meet minimal listing criteria for placement on the deceased donor waiting list (Child-Turcotte-Pugh score of at least 7 for most causes of cirrhosis). Once approved for listing, the patients is prioritized according to the MELD score.[45] This score, based on objective laboratory values, predicts the 3-month mortality of patients awaiting liver transplantation. The MELD score incorporates serum creatinine, bilirubin, and prothrombin time (INR). The formula for the MELD score and 3-month mortality is available on the Internet at www.mayoclinic.

org/meld/mayomodel6.html (Table 2).[46] The driving force of this system is disease severity, and there is no inherent benefit to early listing. In fact, listing too early may waste time and resources and cause the patient anxiety. A MELD score 10 or any complication of portal hypertension is an appropriate indication for transplant evaluation.[43]

If cirrhotic patients have more than MELD score of 30, 3-month survival will be less than 20%, so-called "acute-on-chronic liver failure (ACLF), UNOS 2A" state. The patients show similar clinical findings to ALF, but manifest underlying liver cirrhosis and related portal hypertension. Treatment strategies are timely liver transplantation using good quality graft including deceased donor whole liver or living donor partial liver graft having more than 50% of recipient's standard liver volume and minimal fatty change. At our institution, 16% of the adult LDLT was urgently performed for ACLF patients and the 1-year and 5-year survival rates were 84% and 79% respectively. These successful results indicate that ACLF patients are one of the most appropriate candidates for adult LDLT (Fig. 7).[47]

RECIPIENT OPERATIONS

1. Deceased donor whole liver transplantation[45]

The recipient operation consists of total hepatectomy of the native liver followed by implantation of the donor liver. The native hepatectomy usually begins with division of the ligamentous attachment of the liver, followed by skeletonization of the hilar structures (bile duct, hepatic artery, and portal vein) to prepare for implantation of the new liver. The IVC is encircled above and below the liver to achieve full vascular control. Committing the patient to transplant, diseased liver is removed with retrohepatic IVC. The donor liver is surgically prepared for implantation on the back table, then brought onto the operative field. Anastomoses are constructed between the donor liver and recipient in the following sequence: suprahepatic IVC, infrahepatic IVC, and PV anastomosis. Once the PV is anastomosed, the clamp is removed in sequence and the liver is perfused in PV inflow.

The hepatic artery is typically connected to the recipient hepatic artery with large luminal diameter at the junction of the gastroduodenal artery. Thereafter, bile duct is reconstructed using an end-to-end choledochocholedochostomy. If the recipient bile duct is not appropriate for end-to-end reconstruction, a Roux-en-Y choledochojejunostomy is performed.

2. Living donor liver transplantation

The surgical technique for recipients is based on whole liver resection, with preservation of the IVC removed for whole DDLT.[48] However, it is more sophisticated operation and needs much more careful and delicate dissection than DDLT, because living donor partial liver graft having much smaller-sized hepatic artery, vein and PV should be implanted. For technically successful operation, it is important to make a large and long opening along the sides of the hepatic veins and important to maintain satisfactory portal, biliary and hepatic arterial sources for the reconstruction (Fig. 8).[49] Anastomosis is performed in the following order: hepatic vein, PV and then hepatic artery. The provision of adequate outflow is indispensable for graft function; thus, it is necessary to obtain a wide orifice and an enough length of the hepatic vein for anastomosis.[50] Hepatic arterial reconstruction is technically difficult due to the existence of short, thin and small hepatic arteries on the liver graft, particularly in the East Asian people. The Kyoto group introduced microvascular surgery and report excellent outcomes.[51] It becomes standard technique for hepatic anastomosis cur-

Fig. 7. CT scan showing changes between before and after liver transplantation. (A) HBV-related acute-on-chronic liver failure patient with huge ascites, altered mentality, and high MELD score (40 points). (B) Good regeneration of dual liver grafts is visible and the ascites have disappeared on this 1-month postoperative follow-up CT scan.
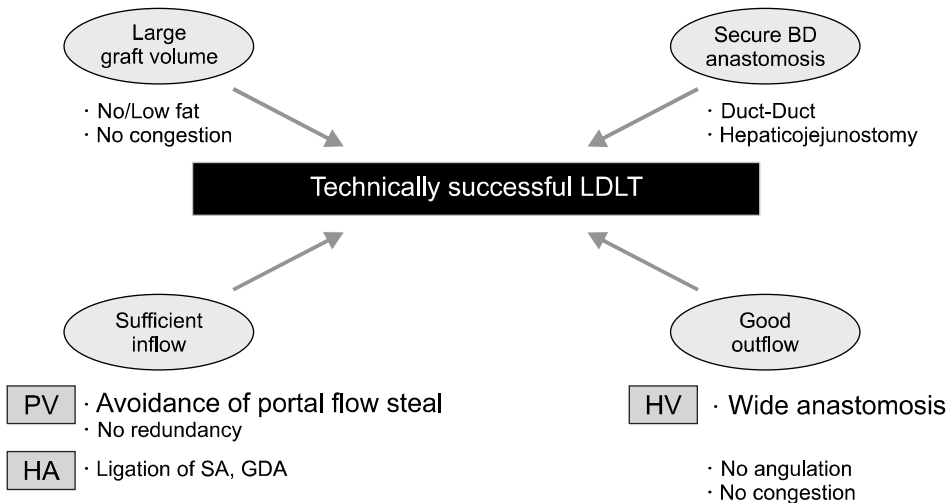
Fig. 8. Interrelationship between graft volume, hepatic inflow and outflow, and bile-duct anastomosis for determining the technically successful living donor liver transplantation (LDLT).

rently.

Bile duct reconstruction is usually performed last. The preferred technique in adult LDLT has been shifted from hepaticojejustomy to duct-to-duct anastomosis.[49] Duct-to-duct anastomosis can preserve physiologic biloenteric and bowel continuity, thus preventing delayed bowel movement, and also allows for endoscopic access to the biliary tree for diagnostic and therapeutic instrumentation and management and prevent ascending cholangitis.[52]

LIVER DONORS

The principal condition for liver donor is ABO blood type compatibility. Histocompatibility is not important for liver transplantation as much as kidney transplantation, and do not determine whether we do transplant or not. Absolute contraindications to organ donation are infectious disease and active malignancy that can cause death of the recipient through transmission. Infectious diseases include Creutzfeldt-Jakob disease, kuru, Gerstmann-Straussler-Scheinker syndrome, and fatal insomnia, HIV virus infection, disseminated and invasive infection by other viruses, mycobacterium, or fungi, and systemic infection by methicillin-resistant staphylococci. However, low grade skin cancer, as basal cell carcinoma, and many squamous cell carcinomas, carcinoma in situ (uterine and cervical), and primary brain tumors without extracranial metastases do not exclude donation.[53,54]

1. Donor selection

1) Deceased liver donor

Selection of an appropriate donor is crucial to the successful outcome of DDLT. Among the most prominent donor characteristics that may influence the development of initial poor function or primary nonfunction in the recipient include old donor age, prolonged ischemia, hypotension and excessive inotropic support, non-heart-beating donors and steatosis.[55] Following characteristics described an ideal liver donor: 50 years or younger; no hepatobiliary disease; hemodynamic and respiratory stability (systolic blood pressure >100 mmHg, and central venous pressure >5 cm/H_2O); an acceptable PaO_2 and hemoglobin level; no severe abdominal trauma, systemic infection, or cancer; diuresis greater than 50 mL/h and normal creatinine; and finally, a dopamine requirement less than 10 μg/kg/min.[56] The critical shortage of deceased donor grafts and the increasing number of recipients awaiting liver transplantation make it extremely difficult to limit organ selection to the use of ideal donors only. The use of donor with extended criteria for organ acceptance has therefore become a necessity in the current era.[57]

Until now, no consensus exists for what an extended criteria donor (ECD) graft is, but typically it refers to grafts more commonly associated with poor function and decreased survival on average. This includes older donors, donation after cardiac death, grafts from individuals infected with HCV, hepatitis B, steatosis and prolonged cold ischemia time.[58,59] Use of ECD increases the pool of available donors and reduces the number of deaths on the waiting list.[60] In an audit of Organ Procurement and Transplantation Network (OPTN) data from over 12,000 recipients between June 2002 and June 2005, 2,873 grafts (24%) were from ECDs. ECD donors are used most commonly for the recipients with low MELD scores (<15)[61] because the combination of high MELD recipients and ECD donors is associated with poor graft function and increased mortality.[58,62] Cameron et al.[62] insisted ECD grafts should not be used for critically-ill recipients such as advanced age and urgent recipients (ALF or ACLF) due to

increment of the risk ratio of death by 50%.

2) Living liver donor

According to Florman *et al.*[63] report, faced with following statistics, death on the waiting list in 2004 was greater than 10%, physicians caring for these patients have endeavored to perform transplants with partial liver grafts from healthy, volunteer liver donors. From this point of view, LDLT was an avoidable and inevitable option for surgeons to treat end stage liver disease patients in the East Asia under extremely rare deceased organ donation regardless of ethical issues about donors.

Organs from living donors offer many potential advantages over organs from deceased donors. The most im-

Table 3. Worldwide Review on Living Liver Donor Mortality Divided in Early (Postoperative) and Late Mortality

#	C-level*	Location	Donor age/sex/graft	Cause of death
	Early			
1	C1	Hamburg (Germany)	29/f/LS	Pulmonary embolism
2	C1	Essen (Germany)	38/m/RL	Liver failure in unrecognized congenital lipodystrophy
3	C2	Jena (Germany)	57/f/RL	Heart failure, multiorgan system failure: LTx, failed
4	C1	Lyon (France)	32/m/RL	Multiple postoperative complication, sepsis
5	C3	Paris (France)	-/-/RL	Myeloma, multiorgan failure
6	C3	- (Europe)	-	Multiple postoperative complications
7	C2	San Antonio (USA)	23/f/LS	Anaphylaxis, anesthesia
8	C1	Chapel Hill (USA)	43/m/RL	Sepsis (venous outflow obstruction, bile leak ?)
9	C1	New York (USA)	57/m/RL	Aspiration, gas gangrene, Clostridium perfringens
10	C3	California (USA)	-/f/LL	Pulmonary embolism
11	C3	- (USA)	-/-/RL	Liver failure
12	C1	Curitiba (Brazil)	31/f/RL	Cerebral bleeding
13	C3	Recife (Brazil)	-/-/LS	Bleeding
14	C3	- (Brazil)	-/-/RL	-
15	C3	- (Brazil)	-/-/-	-
16	C3	- (Argentina)	-/-/RL	Unknown
17	C1	Kyoto (Japan)	46/f/RL	Liver failure, nonalcoholic steatohepatitis; LTx, failed
18	C3	- (Korea)	-/-/RL	-
19	C3	Suwon City (Korea)	56/m/RL	Liver failure, steatosis
20	C1	Hong Kong (China)	50/f/RL	Air embolism, duodenocaval fistula, duodenal ulcer
21	C3	Izmir (Trukey)	28/f/RL	Pulmonary embolism
22	C1	Singapore	39/m/RL	Acute myocardial infarction
23	C3	Cairo (Egypt)	-/m/RL	Sepsis, bile leak
24	C3	Shinbin El Kom (Egypt)	-/-/RL	Liver failure, portal vein thrombosis, bleeding
25	C3	New Dehli (India)	-/-/-	Unknown
26	C3	Hyderabad (India)	52/f/-	Coma after 48 hours, remained in vegetative state; died
	Late			
1	C2	Unknown (USA)	35/m/RL	Train accident
2	C2	Unknown (USA)	50/m/RL	Suicide, gun shot wound; bipolar disorder
3	C1	Philadelphia (USA)	36/f/LS	Illicit drug overdose
4	C1	Los Angeles (USA)	35/m/RL	Recreational drug overdose, suicide (23 months later)
5	C3	Unknown (Europe)	-/-/-	Budd-Chiari syndrome
6	C1	Hamburg (Germany)	30/m/LS	Amyotrophic lateral sclerosis (3 years later)
7	C2	Kyoto (Japan)	36/m/LS	Unknown (3 years later)
8	C2	- (Japan)	-/m/-	Unknown (10 year later)

f, female; m, male; LS, lateral segment; LL, left lobe; RL, right lobe; LTx, liver transplantation.
*Certainty (C) level based on the source of information
C1, Donor death documented, confirmed, and published in the medical literature by an author representing the transplant center where the fatality occurred; evidence based on direct information; details of the case often provided, e.g., donor age, sex, graft type, date of surgery, cause of death, date of death, survival; C2, Donor death not clearly identified, confirmed or published by transplant center where the fatality occurred; transplant center usually not identified; indirect evidence obtained from secondary publications by other authors or reviews; eventually some information about the case provided; C3, Donor death not identified, confirmed or published; transplant center not identified; evidence based on verbal presentation or personal communication; no further details of the case provided.
Reprinted from Ringe B, Strong RW. The dilemma of living liver donor death: to report or not to report? Transplantation 2008;85:790-793.

portant advantages of living donation are that it optimizes the timing of transplantation and frees patients from the waiting list. Secondly preservation time is minimal, so there is significantly less ischemic damage to the liver. Therefore, the quality of the donated liver is much better. Most importantly, LDLT increases the global pool of transplantable organs, allowing more people to get transplantation as a life-saving therapy.

There are, however, a number of disadvantages to LDLT which must be considered carefully. The donor, a perfectly healthy volunteer, faces unequivocal risks of morbidity and even mortality. To date, more than 12,000 living donor hepatic resection have been performed worldwide (ELTR, UNOS, CM Lo, pers. comm., 2006: mortality approaches 0.5% for the right lobe donor in contrast to approximately 0.1% for left lobe donation).[64] Table 3 summarizes the worldwide reported donor's mortalities collected from the international literature and from recent reports at professional society meetings.[65] Additionally, two donors have required liver transplantation for themselves as the result of operative complications.[63]

LDLT also carries certain increased risks for the recipients. It is technically more complex than deceased whole liver transplantation. The incidence of biliary complications increased with partial grafts. In addition, the small-for-size syndrome is essentially seen only with partial grafts, when the recipient does not receive enough functional liver mass. Finally, LDLT procedures are considerably more labor-intensive efforts and prone to result in more postoperative complications related to short and small hepatic artery, vein, PV and bile ducts (Table 4).
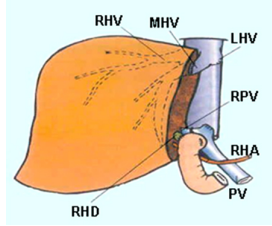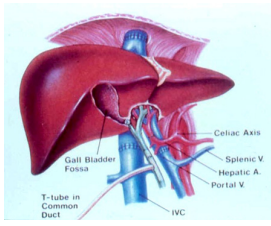
To be a successful LDLT, appropriate donor evaluation is one of the most crucial parts.[66] The goal of evaluation process is to exclude donors with an increased risk for morbidity and mortality, while at the same time assuring that a suitable graft for the recipient can be obtained. The person who is willing to be a living liver donor, should satisfy the following guiding ethical principles including altruism, the absence of coercion or monetary reward, patient autonomy, beneficence, and nonmaleficence.[67] Additionally, he is fully informed of the risks and benefits as a donor, and fully informed of the risks, benefits, and alternative treatment available to the recipient,[68] because donor safety is utmost important issue. There can be no exceptions to this rule, regardless of the consequences for the recipient, even death.

Most living donors are in excellent health. Although there is no definitive age cutoff, typically ages between 18 and 55 years are preferred.[65] At our institution, upper age limit is 60 years, but biological age is more important than donor's chronologic age. However, careful caution is necessary for older age donor (>50 years) who is associated with a fourfold risk of complications.[69] Lower age limit can be lowered to 16 years only when the recipient is the donor's parent.[19]

Fatty liver is dangerous for both donor and recipient. The Vancouver Forum participants[64] suggested that donor liver biopsy should be performed if blood specimen liver tests are abnormal and if steatosis or other abnormalities are noted on imaging studies. Additionally, the histological findings that should preclude living liver donation were also clearly defined during Forum. They include (i) portal or sinusoidal fibrosis, (ii) nonalcoholic steatohepatitis, (iii) steatosis >20% (only for right liver), and (iv) portal inflammation or necroinflammatory changes.[64] Liver

Table 4. Differences between Adult-to-adult LDLT and DDLT

	Adult-to-adult LDLT	DDLT
Operation		
	Complex	Simple
Recipient's complication (particularly in bile duct)	High	Low
Liver graft size	Sometimes "Small-for-size"	Enough
Liver graft quality	Good	Sometimes "Poor"
Donor's complication	Morbidity: 16 to 32% Mortality: 0.4%	Zero
Donor's source	Private gift	Public resource

LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation.

biopsy could unveil unexpected liver pathology (as high as 21%),[65] and body mass index is an inaccurate indicator of steatosis, so many centers advocate routine liver biopsy in the donor evaluation protocol.[70] In our experience, routine application of preoperative donor liver biopsy make us avoid invalid donor operation,[19] and biopsy related donor complication has been minimized with help of the hands of experienced practitioner coupled with careful post-biopsy observation. If the transplant is not urgent, we recommend the potential donor with liver steatosis to reduce body weight and to perform vigorous exercise. Successful reduction of liver steatosis is possible and donation is acceptable.[71]

Regarding to ABO blood type in LDLT, identical or compatible ABO blood type between recipient and donor is recommended; however, ABO incompatible blood type LDLT has been undertaken successfully in special instance such as infant < 1 year of age without presence of isoagglutinins, and in emergency situations where no deceased donor allograft is available.[72] Recently, the group of Kyoto,[73] Chicago,[74] and Gent[75] demonstrated the feasibility of adult LDLT across ABO barriers by using different approaches and immunosuppressive protocols. At our institution, the liver donor-exchange program for adult, as in kidney transplantation, has performed to overcome blood group mismatching in 5 donor-recipient pairs since 2003, and also started ABO incompatible adult-to-adult LDLT successfully in 2008.[19]

By definition, a living donor is a completely healthy person. It is the consensus that potential donors with concomitant medical illness should not be allowed to donate.[70] However, the presence of mild systemic disease, such as well controlled mild hypertension or diet-con-

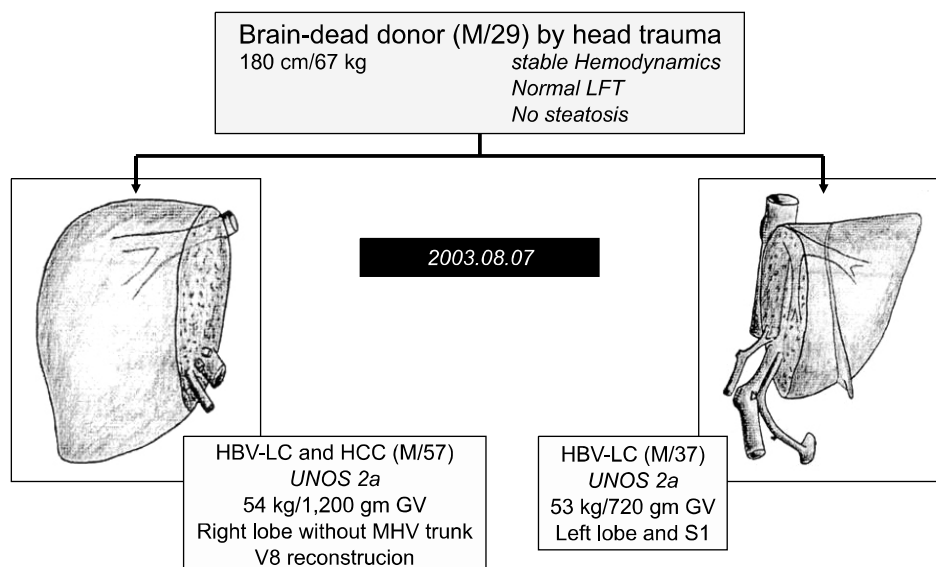trolled diabetes, is not necessarily a contraindication to donation.[76]

Extensive blood tests are considered necessary to detect HIV, HCV, or hepatitis B virus (HBV) infection, and laboratory testing for a preexisting hypercoagulable condition especially if the potential donor has a history of venous thrombosis.[64,77] The HBcAb positive donor can donate for a recipient affected by HBV-cirrhosis and HBV naïve recipient also with prophylaxis of hepatitis B immunoglobulin.[19]

Imaging study of the liver is needed to exclude parenchymal liver disease, to identify the vascular and biliary anatomy and to estimate the graft and remnant liver volume. As a 'all in one' procedures to simplify and shorten such time-consuming and costly procedure, use of multidetector CT is helpful to evaluate them in a single diagnostic study,[78,79] and is better than magnetic resonance imaging in the ability to accurately assess the biliary anatomy.[78] It is generally believed that a remnant liver of at least 30% of the original liver volume with complete venous drainage is safe for donor survival and a graft that provides 40% of the estimated standard liver volume[80] or 0.8% of the body weight of the recipient is necessary for the recipient recovery.[19,64,81] Volumetric imaging analysis may overestimate the actual liver volume by as much as 10%. The main cause of the overestimation is related to the difference between the vital liver filled with blood *in vivo* and the graft that is in a state of collapse *ex vivo*.

2. Donor procurement

1) Deceased liver donor

Whole organ procurement is now a well described

Brain-dead donor (M/29) by head trauma
180 cm/67 kg   *stable Hemodynamics*
                      Normal LFT
                      No steatosis

2003.08.07

HBV-LC and HCC (M/57)
UNOS 2a
54 kg/1,200 gm GV
Right lobe without MHV trunk
V8 reconstrucion

HBV-LC (M/37)
UNOS 2a
53 kg/720 gm GV
Left lobe and S1

Fig. 9. Split liver transplantation to two adult recipients in order to expand the donor pool at Asan Medical Center. This is the first time that this procedure was performed in Korea, in August 2003.

procedure. The principles of minimum mobilization to define vascular structures, *in situ* perfusion with 4°C preservation solution, and sequential en bloc harvest of organs yield good allograft preservation.

"Split liver" grafting involves the preparation of two allografts from a single donor.[82] In most cases, the extended right lobe allograft (segment 4-8) is used in an adult or large child, while the left lateral segment allograft (segment 2,3) is transplanted into a small recipient. At our institution, split liver transplantation for two adult recipients has been performed successfully to more than 16 adult recipients.[83] The whole liver is divided into right lobe without middle hepatic vein (MHV), same to modified right lobe graft in LDLT, and left liver with IVC and common hepatic artery by using *in situ* or *ex vivo* technique (Fig. 9).

2) Living liver donor

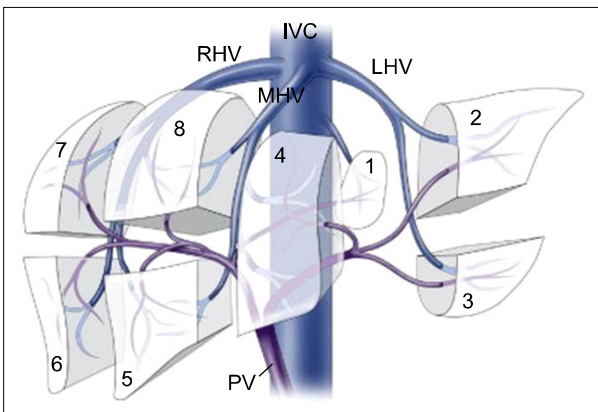The performance of LDLT relies on an understanding of

Fig. 10. Segmental anatomy of the liver using the Couinaud's segments. Reprinted from Brown RS Jr. Live donors in liver transplantation. Gastroenterology 2008;134:1802-1813.

the vascular and biliary anatomy of the liver. The left hepatic lobe consists of left lateral sector (Counaud segment 2 and 3) and medial sector (Counaud segment 4); and Counaud segment 5,6,7 and 8 compose the right hepatic lobe (Fig. 10). Counaud segment 1 is the caudate lobe. For most people the left lateral sector comprise 20% of their total liver volume, the left lobe 40%, and the right lobe 60%. In general, the common grafts that can be used from a living donor for transplantation include the left lateral sector, the left lobe (with or without caudate lobe), and the right lobe (Fig. 11).

The argument for the need of including the MHV in right lobe graft continues ever since its inception. Hong Kong group advocates for right lobe with MHV. They believe that MHV is the important drainage vein of segments 5 and 8, and sometimes 6.[84,85] Right lobe graft without MHV will lead to graft congestion, drainage of hepatic artery blood via the right anterior portal vein, persistence of portal hypertension, and excessive blood flow into the right posterior sector leading to serious graft damage. However, the most important shortcoming of this liver graft is hampering the donor safety (Fig. 12). Actually graft type of the donor deaths after liver donation from Hong Kong, Japan, and Korea were all right lobe with MHV grafts.[65] In addition, the majority of programs in the United States shows that this is too large a liver resection for a healthy donor, who does not essentially require surgery, and increase the risk of small-for-size syndrome and the subsequent postoperative liver failure in the donor.[76] Marcos *et al*. advocates for right lobe without MHV, because donor safety could be ensured, intrahepatic venous collaterals are present in between the middle and right hepatic vein branches,[86] and the incidence of graft congestion is very low. However, collaterals between the right hepatic vein and MHV are small and late in development and are not present in every
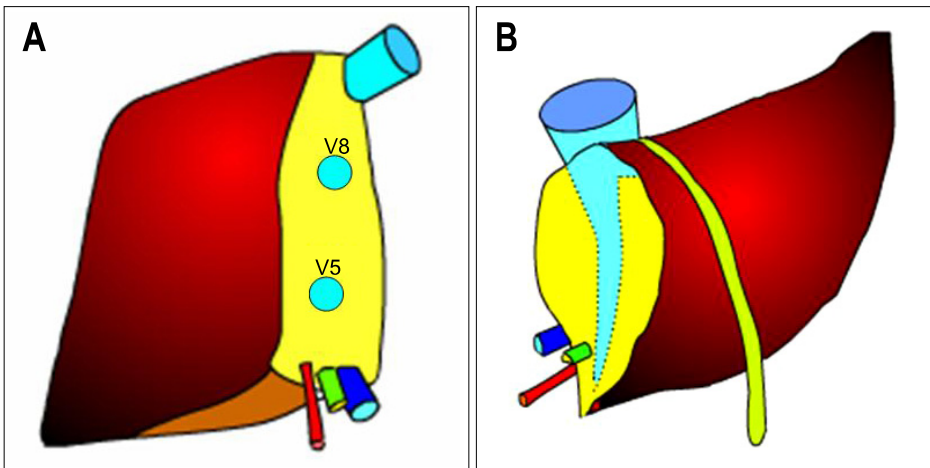

Fig. 11. Most commonly used graft for adult-to-adult LDLT. (A) Right lobe graft, (B) Left lobe graft.
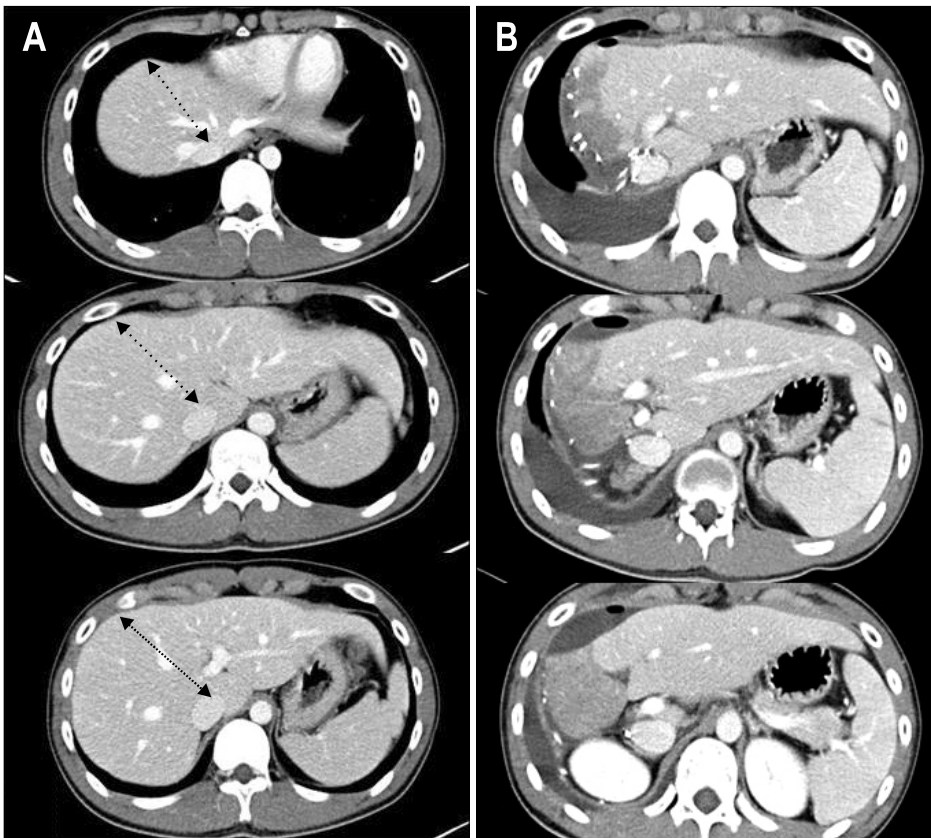
Fig. 12. Congestion of the medial sector after procurement of the right lobe with a middle hepatic vein graft from a living liver donor. (A) Preoperative CT scan showing the donor liver and imaginary parenchymal transection line when the right lobe with the middle hepatic vein graft is harvested. (B) CT scan made on the 7th postoperative day, revealing a large area of congestion at the medial sector.
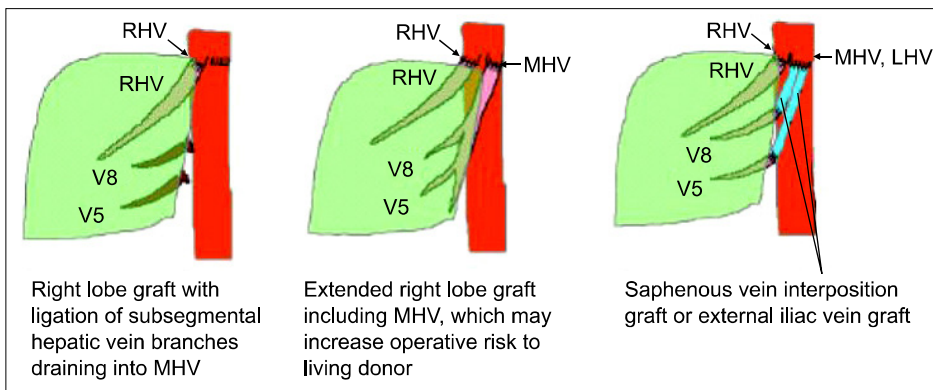

Fig. 13. A scheme for modified right lobe (MRL) liver grafting. RHV, right hepatic vein; MHV, middle hepatic vein; LHV, left hepatic vein; V5, hepatic venous tributaries from segment 5; V8, hepatic venous tributaries from segment 8.

case.[87] Lee *et al.* noted world first about the importance of congestion and its drainage in the anterior sector of right lobe graft without MHV,[87] and initiated modified right lobe graft, which is right lobe graft without MHV but restoring the continuity of sizable segment 5 and 8 (≥5 mm) venous drainage in the graft by using venous conduit (Fig. 13).[17,88] After clinical application of this graft type, 6-months recipient survival rate improved from 71% to more than 90% at our institution.[89] In some rare instance, right posterior sector (Counaud segment 6,7),[90] and monosegment graft have been used.[91]

During recipient and donor workup for adult LDLT,

heartbreaking cases who can not be transplanted from a single donor due to graft-recipient size mismatching, unacceptable right-to-left lobe volume discrepancy and excessive hepatic steatosis, are not uncommon. Under those circumstance, Lee *et al.* has performed dual-graft adult LDLT in which two left liver (left lateral sector or left lobe) grafts are procured from two donors and implanted in one recipient, in order to achieve maximal donor safety through minimal resection of liver mass while increasing recipient actual graft volume (Fig. 14).[19,92,93] Sometimes right lobe or right posterior sector graft also has been used for right-sided liver graft of dual-graft LDLT because
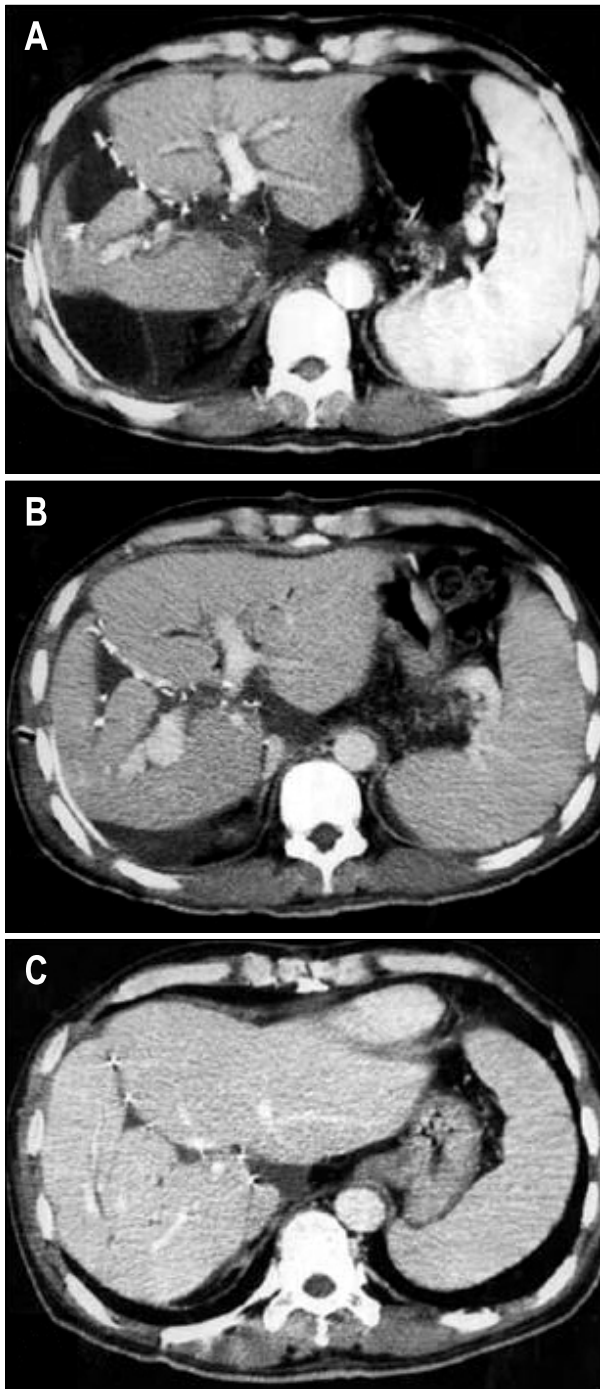
Fig. 14. Postoperative follow-up CT scan of the recipient, demonstrating the balanced regeneration of both liver grafts. (A) CT scan taken 5 days after transplantation showing that the second left lobe graft in the right upper abdomen was still small and supported by a tissue expander bag. (B) CT scan made 2 weeks after transplantation, showing the rapid regeneration of both grafts. (C) CT scan made 2 months after transplantation, showing that two regenerated left lobe grafts were in the shape of a normal liver.

of the recipient body size or anatomic variation of donor liver (Fig. 15). At our institution, various types of single liver graft together with dual-grafts has been used to satisfy both donor safety and recipient metabolic demands (Fig. 16).

As an incision line for all types of donor hepatectomy, a right subcostal incision with midline extension is adequate and spares the donor morbidity of dividing the rectus muscle bilaterally.[63] In addition to conventional open techniques, Cheriqui *et al.*[94] reported for the first time laparoscopic left lateral sector retrievals for pediatric LDLT. Recently at our institution also, laparoscopic left lateral sector donor hepatectomy has been performed routinely for pediatric LDLT. Intraoperative cholangiography by using a radio-opaque marker tagging method and direct bile duct probing through the cystic duct was routinely used to identify an adequate location for bile duct division, minimizing the number of graft duct openings obtained from various donor bile duct anatomies.[95] For the parenchymal transection, ultrasound or water-jet dissector are generally used in combination with electrocautery under without hilar occlusion or using only intermittent clamping.[96] Graft retrieval is performed without portal cannulation in donor's abdominal cavity. Pinching of the portal vein wall with the cannula *in situ* or pushing the tube into the right anterior or posterior PV is efficient for uniform flushing of the liver graft. The need for hepatic artery flushing by preservation flushing is controversial. Finally, in case of modified right lobe graft, vascular conduits using recipient's great saphenous vein, PV, umbilical vein, or cryopreserved cadaveric vessels are employed to establish the good outflow of the graft.[88,97,98] In case of right lobe with MHV, Hong Kong group preferred to perform venoplasty of the right hepatic vein/ MHV to form a large triangular orifice.[99] At our center, however, quilt venoplasty using recipient's graft saphenous vein and cryopreserved vessels is used to make a large single orifice.[100] Before wound closure, the left liver remnant should be anchored to the anterior abdominal wall to prevent its rotation into the right subphrenic cavity and subsequent outflow obstruction.[101]

IMMUNOSUPPERSSION AFTER LIVER TRANSPLANTATION

After introduction of cyclosporine, a number of new immunosuppressants (tacrolimus, mycophenolate mofetil, sirolimus, interleukin-2 receptor blocker, humanized monoclonal antibody, etc) are available currently. Large series describing results from the previous years mention acute rejection in 40 to 60% of liver transplant patients.[102,103]
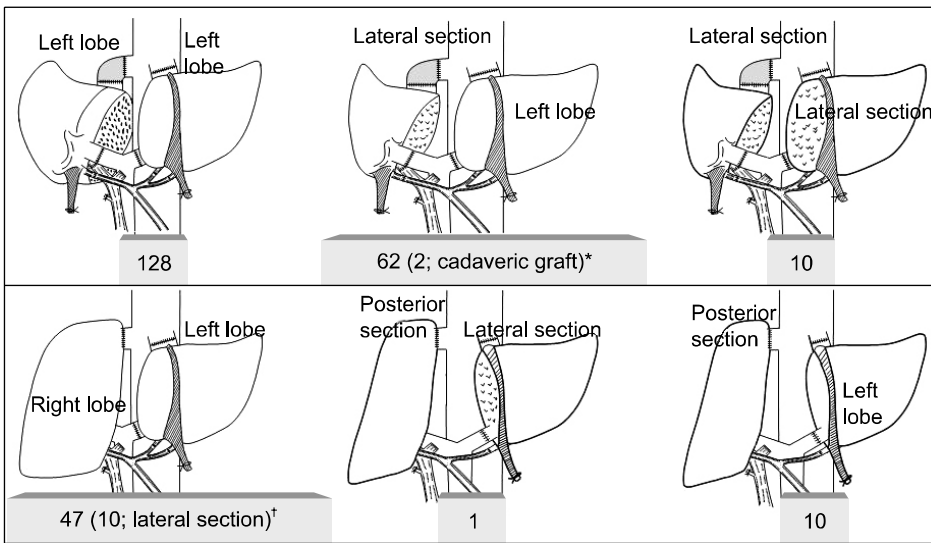
Fig. 15. Two hundred and fifty-eight dual-graft adult-to-adult LDLTs were performed between March 2000 and December 2008 at the Asan Medical Center. *Two recipients received a left lobe from a live donor and a split lateral segment from a deceased donor, respectively, on June 2000 and December 2008, respectively; [†]Right lobe (from wife) and left lobe (from cousin) dual-graft adult-to-adult LDLT for a large-size recipient was performed successfully in April 2001. Lateral section replaced the left lobe in 10 of 47 recipients.
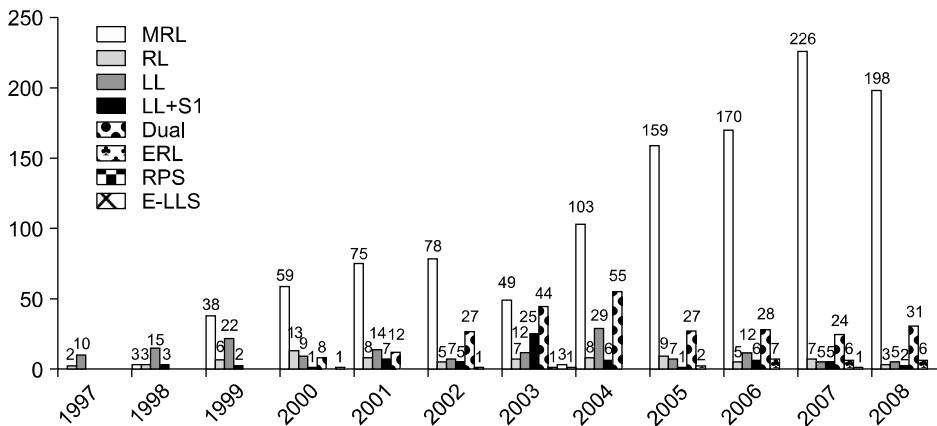
Fig. 16. Types of graft in 1,739 adult-to-adult LDLTs.
MRL, modified right lobe; RL, right lobe; LL, left lobe; S1, caudate lobe; ERL, extended right lobe; RPS, right posterior sector; E-LLS, extended left lateral segment.

More recent data from USA for 2003 show acute rejection in as few as 18% of patients (www.unos.org). Vast majority of patients can be treated satisfactorily with boluses of steroids. Chronic rejection is a rare event in liver transplantation, occurring in less than 5% of patients.[104]

In the majority of liver transplant recipients, combination of two or three different maintenance immunosuppressive drugs is used for prevention of rejection. The calcineurin inhibitors tacrolimus and cyclosporine are the mainstays of immunosuppression in liver transplantation. Over 95% of patients are discharged with a calcineurin inhibitor as a primary immunosuppressant, with tacrolimus being most frequently used (www.unos.org).

Steroids are still almost universally used after liver transplantation. Most patients are discharged with steroids, which are subsequently tapered and weaned in the following months.

Mycophenolate mofetil (MMF), which is antimetabolites such as azathioprine, is also frequently used to reduce calcineurin inhibitor dose and to prevent or limit side effects such as renal dysfunction, hypertension and hyperlipidemia. UNOS data show that 60% of patients are discharged from the hospital on the use of MMF, same in our institute.

Sirolimus (Rapamycin) is a new immunosuppressive agent, which is structurally similar to tacrolimus, and has antifibrotic and antineoplastic characteristics, but lack of nephrotoxicity. However, severe side effects, including delayed wound healing and vascular complications limit its clinical usage.[105] In general one can say that currently the most important challenge with regards to immunosuppression in liver transplantation is not to find drugs that are more powerful, but drugs that are less harmful. In the mean time, the present availability of a wide spectrum of effective and specific immunosuppressive drugs allows individualized selection of drugs, thereby limiting serious

side effects.[25]

COMPLICATIONS

1. Early post-transplant complications

Postoperative technical and organic medical complications, primary dysfunction, graft rejection and infections are the major short-term complications (Table 5).[106]

During the initial 48-72 postoperative hours, abnormal liver biochemistries are typical and reflect a number of insults to the graft, including following harvesting, preservation, and subsequent reperfusion. However, daily routine Doppler ultrasound exam should be performed to exclude vascular complications such as hepatic artery thrombosis, portal and hepatic vein stenosis or obstruction.

Biliary complications are considered the Achilles' heel of LT, particularly in the setting of LDLT. The rate of bile leak or stricture at the anastomotic site or cut edge of the transected liver, were reported in 15-60% of recipients in early, single center reports.[76] At our institution, cumulative biliary complication rate after LDLT rose to 20.2% in 5 years, and most stenosis was successfully treated using radiologic intervention.[107]

Within the first week after LT, liver biochemistry steadily improve as ischemia and reperfusion damage resolves, and also the volume of transplanted liver graft is regenerating. Acute rejection becomes an important and frequent cause of graft dysfunction at 1 week and beyond. Liver biopsy is necessary for confirmatory diagnosis.

Various infectious complications following liver transplantation can occur, and opportunistic infections related to intensive immunosuppresion are relatively common such as cytomegalovirus, Pneumocystis carinii, and fungal

Table 5. Allograft Dysfunction and Surgical Complications Occurring in the Immediate Postoperative Period

Allograft dysfunction
Primary non-function
Primary poor function
Acute cellular rejection
Recurrent viral hepatitis
Drug hepatotoxicity
Surgical complications
Postoperative hemorrhage
Vascular complications
Hepatic artery thrombosis
Portal vein stenosis or obstruction
Hepatic vein stenosis or obstruction
Other
Biliary tract complications
Bile leak or fistula
Biliary stricture

infection.

Neurologic dysfunction, hyperglycemia and renal impairment can occur mainly related to the toxic effects of cyclosporine and tacrolimus.

2. Long-term complications

Today, with improved survival in most transplant centers, increasing attention is being given to complications that develop in the long-term, and that are highly related to the immunosuppressive treatment. The most frequent complications are chronic renal failure, hypertension, diabetes mellitus, dyslipidemia, obesity, bone or neurological complications, development of de novo tumors.[108]

Impaired renal dysfunction before transplantation, chronic use of calcineurin inhibitors and hypertension probably all contribute to the increased risk for chronic renal failure after liver transplantation. The cumulative risk of renal failure has been described to be as high as 20% five years after transplantation.[109] Strenuous management of hypertension and withdrawal or reduction of calcineurin inhibitors in an early stage should be considered.

Hypertension, diabetes, hyperlipidemia, and obesity, which are well-known risk factors for cardiovascular disease, occur in up to 75%, 15%, 40-60%, and 30-70% of patients, respectively, long-term after transplantation.[110,111] This increase in risk factors is at least partly due to continuous immunosuppressive drugs. This combined with high risk behavior leads to a markedly increased risk for arthrosclerosis and subsequent cardiovascular events.[112] Vigorous screening for cardiovascular risk factors and aggressive management is essential for all liver transplant recipients.

Increased risk for osteoporosis in liver transplant recipient results from the combination of low bone mineral density before transplantation due to hepatic osteodystrophy, malnutrition and inactivity and steroid use after transplantation.[112] In the present era, with lower dosages of corticosteroids and the availability of bisphosphonates, bone disease can be prevented and treated easier than the earlier era.

Varying degree of neurological complications develop in large proportion of liver transplant recipient mostly secondary to calcineurin inhibitor. Tremor is the most common symptom, and headache, paresthesia, or insomnia is other complaints that can be actually very disabling. Reduction of immunosuppressive drug dose might be helpful.

De novo malignancy has an incidence of 5-16% in different series.[113] It is a major cause of late death in liver transplant recipients.[114] There is irrefutable evidence of an increased incidence of skin, cervical, and lymphoid tumors

after liver transplantation.[115] The incidence of oropharyngeal, esophageal, lung, throat, and tongue cancer may also be increased.[116] The contributors to this increased risk are high-risk behavior before transplantation (smoking, alcoholism) and the life-long use of immunosuppressive drugs. Consequently, post-transplant management should focus on the elimination of risk factors, as well as minimizing the amount of immunosuppression.

RECURRENT DISEASE AFTER TRANSPLANTATION

In the early 1990s hepatitis B recurrence was observed more than 80% of liver transplant recipients. Currently, effective antiviral prophylaxis with high dose hepatitis B immunoglobulin has virtually eliminated HBV recurrence.[117] Overall survival of patients transplanted for HBV-related cirrhosis currently exceeds 90% at one year and 85% at 5 years.[23]

Recurrence of hepatitis C is almost universally seen. It usually presents gradually in the postoperative courses, but accelerated compared to the pretransplant setting. Protocol biopsies done 5 years after transplant showed that 20% of patients transplanted for HCV already had evidence of allograft cirrhosis.[118] During recent years, however, improved survival of patients transplanted for HCV has been seen, with a 10-year patient survival of approximately 60%.[119] Recent study using combination of ribavirin and pegylated interferon for recurrent HCV patients after LT showed some promising preliminary results.[120]

Recurrence of HCC is especially common in patients with a poorly differentiated tumor or macroscopic vascular invasion.[120] Various treatment including surgical resection, transarterial chmoembolization, radiofrequency ablation, chemotherapy, and radiotherapy, should be performed for recurrent HCC. The outcome is universally dismal, but long-term survival is possible in a few selected cases received radical treatment.[121]

Recurrence of autoimmune disease in an organ from a donor is immunologically intriguing. Diagnosis can be difficult due to other potential causes for graft dysfunction. Recurrence of an early stage of primary biliary cirrhosis may occur in a majority of patients transplanted for this indication in the long term, but seldom leads to cirrhosis.[122]

Recurrence of autoimmune hepatitis is seen in 22% of patients, and is treated as in nontransplant patients.[123] Recurrence of primary sclerosing cholangitis occurs in about 11% of patients,[123] diagnosis may be difficult because of overlap with nonanastomotic strictures from other causes.

Retransplantation for recurrent disease is a difficult ethical issue faced by transplant teams in an era of intractable organ shortage. Perioperative risk, survival, quality of life, as well as the presence of comorbidities such as renal failure related to immunosuppression toxicity all need to be weighed in the decision to retransplant.[43]

RECIPIENT OUTCOMES

The survival rates after DDLT are expected more than 85% and 75% at 1-year and 5-years post-transplantation, respectively.[124] The survival rate after LDLT was much lower than DDLT at the time of beginning. However, LDLT has evolved to be a valuable strategy in reducing waiting list mortality for pediatric patients and adult patients with chronic liver disease, ALF and HCC. In the East Asia including Korea, Japan, Hong Kong, where deceased organ donation is very rare, marked improvement of graft survival around 85% had achieved with help of accumulation of knowledge about portal inflow modulation, adequate graft size and venous outflow drainage, and technical innovations in LDLT during early period of 2000s.[17,125,126] A recent retrospective analysis of the Adult-to-Adult LDLT cohort study (A2ALL) group clearly showed, that graft failure rate correlated with experience; i.e., centers with more than 20 LDLT had a significantly lower graft failure risk.[126] Accordingly, more recent studies reported similar patient survival rates among living donor and deceased donor liver transplant recipient.[61,127,128] A2ALL consortium and from UNOS data base, however, showed that LDLT was not the most appropriate solution for the patients with a MELD score >30, so-called, ACLF or chronic liver disease with severe decompensation,[129,130] because the post-transplantation survival rates are poor (57%), compared to 82% survival rate in deceased donor liver transplant recipients who were on same severity.[131,132] Recently patient survival rate after adult LDLT at our institution is 90.7% and 85.2% at 2-year and 5-years post-transplantation,[19] and A2ALL's recommendation for ACLF patients is invalid because our large LDLT series showed 84% and 79% survival rate for high MELD (>30) recipients at 1-year and 5-years post-transplantation,[47] comparable results to DDLT.[131] It could be only possible with the technical refinement by transplant surgeons and the 24 hours intensive postoperative care by dedicating young surgeons, because postoperative courses of LDLT using partial liver graft is a dynamic process necessitating rapid graft regeneration and it can cause unpredictable disastrous events more frequently than DDLT.

CONCLUSIONS

Liver transplantation has revolutionized the management of acute and chronic liver diseases. The scarcity of donor organ is still the factors limiting its use. Expansion of the donor pool with increasing use of extended criteria organs has increased greatly over the last few decades. In the East Asia, LDLT has been a good alternative to DDLT regardless of disease severity and currently the outcome is not different between them. With improved survival in most transplant centers, increased attention should be given to complications that develop in the long-term.

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