Background

The techniques of living donor liver transplantation (LDLT) developed rapidly in the 1990s to compensate for a severe deficiency in the availability of liver grafts from cadaveric donors for the treatment of patients with end-stage liver disease. This tendency was particularly prominent in East Asia, as brain-death donors have remained largely unavailable for a variety of reasons. Thanks to refinements in surgical technique and postoperative management for LDLT, the cumulative total of LDLTs in East Asian countries has exceeded 2000 and, importantly, donor mortality has yet to be encountered. Moreover, indications for LDLT have been successfully expanded from paediatric to adult cases, following the introduction of right lobe graft. The significance of LDLT under conditions of limited opportunities for cadaveric liver transplantation, as experienced in these countries, differs significantly from that seen with the numerous opportunities for cadaveric donors in Europe and the USA. This review describes not only the experiences of East Asia, but also the specific differences from Western countries, such as indications, graft size issues and ABO blood type combinations, to shed light on the future of liver transplantation.

Keywords
liver transplantation, living donor, Eastern experience

Introduction

Liver transplantation became well established in Western countries in the 1980s, following the introduction of cyclosporine in 1979 [1, 2]. The number of liver transplant candidates rapidly increased throughout this period, leading to a serious shortage of grafts in many transplant centres in Europe and the USA. Conversely, many Asian countries did not see the introduction of cadaveric organ transplantation until the 1990s, due to issues as varied as religious and ethical opposition, debate over the definition of brain death, and public opinion. To overcome these obstacles, living donor liver transplantation (LDLT) was introduced in Japan, and spread to Korea, Taiwan, Hong Kong and other Asian countries. The LDLT technique has recently been re-evaluated and has become an important option for end-stage liver disease even in countries where cadaveric liver transplantation has long been utilised.

LDLT was originally used exclusively in small children, but the indications have gradually been extended to larger and older children, small adults, and finally to all adults. Concomitant with this expansion, liver graft has shifted from the left to the right side.

In this article, the history of LDLT is reviewed with respect to Eastern countries, where cadaveric organ donation remains extremely sporadic, and the current problems and potential solutions are discussed.

Asian survey

Living donor versus cadaveric liver transplant

Compared with the rapid growth of liver transplantation in Western countries, liver transplantation in Asia did not become well accepted until the early 1990s. Many factors contributed to preventing the spread of organ transplantation in Eastern countries. None of these were due to lack of the requisite surgical skills, but rather can be attributed to a lack of understanding about transplantation by the public. Religious opposition arose from issues such as the definition of brain death, while ethical debate centred on details such as the procurement of transplant organs from donors who had not suffered cardiac death. Changing public perceptions of transplant harvesting from cadaveric donors is difficult, and proved an insurmountable obstacle at that time. Liver transplantation from living donors offered the most obvious
means to circumvent this complete lack of transplant organs in Asian countries, and had been successfully pioneered by Strong and colleagues in Australia [3]. In 1990, the first LDLT in Asia was performed by Nagasue and colleagues in Japan [4], followed by the Kyoto University Team [5] and others. Liver transplantation in Asia increased dramatically throughout the 1990s following this breakthrough method (Figures 1 and 2).

While LDLT programmes were rapidly disseminated into Asian transplant centres, liver transplantations from cadaveric donors remained severely limited. Laws defining brain death were enacted in Taiwan (1987), Singapore (1987), the Philippines (1992) and Japan (1997). Numbers of organ transplantations from cadaveric donors were disappointingly small compared with Western countries (Figure 2). For example, 502 liver transplantations from living donors were performed in the USA in 2001, compared with 5108 from cadaveric donors. Conversely, Asian countries performed 541 LDLT and only 213 cadaveric liver transplantations in 2000. Asian transplant centres are obviously still extremely dependent on LDLT as the primary source of liver grafts.

Dependence on LDLT does, however, vary in each country (Figure 3). Japan remains the country most...
dependent on LDLT (99.2%), followed by Korea (65.8%) and Taiwan (36.5%), whereas the Philippines and Singapore are less dependent on LDLT. The survey, which was performed by Furukawa in April 2001 among 51 major Asian transplant centres, revealed that more than three-quarters (78.8%) of liver transplantations were derived from cadaveric donors in China.

**Shift of living donor graft type**

The concept of using living donors for children awaiting hepatic transplantation was first entertained more than a decade ago [3, 6]. The initial repertoire for LDLT grafts comprised left lateral segment graft, extended left lateral segment graft and left lobe graft with middle hepatic vein (MHV), all of which entail similarly small surgical risks to donors. Extension of indications from small children to larger and older children was therefore rather smooth. The next major step was application of the procedure to large adolescents and adults. At this stage, the problem of small-for-size graft was encountered, with associated poor early graft function, hepatocyte injury and, most importantly, reduced patient survival. Overcoming this difficulty required the use of larger hepatic grafts, necessitating right lobe graft. Right lobe graft was introduced by the Kyoto Team in 1994 [7], and the procedure was applied to adult-to-adult LDLT by the Hong Kong Team in 1996 [8]. The treatment modality now covers a wide range of patient body sizes, enabling the indications for LDLT to be expanded yet again. Naturally, the number of LDLTs in Asian countries increased substantially following the introduction of adult-to-adult right lobe LDLT to Korea (1997), Japan (1998) and Taiwan (2000) (Figure 4). However, left lobe with caudate lobe graft is still an option for adult-to-adult LDLT in some institutions [9].

**Indications for living donor liver transplantation**

According to a survey involving five major centres (Kyoto University, Japan; Tokyo University, Japan; Asian Medical Center, Korea; Chang Gung Memorial Hospital, Taiwan; and Queen Mary Hospital, Hong Kong), the two major indications for LDLT are biliary atresia (37%) and hepatitis B-related liver disease (28%) (Figure 5). LDLT for biliary atresia is now such a well-established procedure that no discussion is needed. On the other hand, over 300 million people worldwide have chronic infection with hepatitis B virus (HBV), and more than 75% of these are of Asian origin (Figure 6) [10, 11]. Many countries have reported dramatic reductions in the prevalence of chronic HBV infection among children born since the introduction of hepatitis B vaccine into infant immunisation schedules, but those already infected and displaying viral replication are at the highest risk of progressive liver disease, marking them as candidates for liver transplantation. Prophylaxis against the recurrence of hepatitis B following LDLT can be achieved either by combination therapy with hepatitis B immunoglobulin and lamivudine, or by monophylaxis.
Standard therapies vary with institutional protocols, but satisfactory outcomes are generally achieved.

Hepatocellular carcinoma (HCC) represents a controversial indication for both cadaveric liver transplantation and LDLT. The Milan criteria, which are well accepted in Western countries [12], have shown excellent results with a low risk of recurrence. However, the Milan criteria were designed for cadaveric liver transplantation and take into account the organ allocation system to maximise organ utilisation. In contrast, liver grafts from living donors are not public resources, but private gifts to patients. Given this difference in the nature of liver graft resources, the Milan criteria might not be suitable for application to indications for LDLT.
Several transplant institutions in Asia have expanded their indications to include advanced HCC with no detectable extrahepatic metastasis or vascular invasion on preoperative image studies, irrespective of tumour size or number. Kyoto University had performed 56 LDLTs on patients with HCC by March 2002, and overall survival rates were 71% and 67% at 3 years among patients who fulfilled (n = 31) or did not fulfill (n = 25) the Milan criteria, respectively. Despite these results, better HCC indications are being sought for LDLT to achieve improved outcomes.

Clinical outcomes
With the technical refinements in surgery and post-transplant management, outcomes following LDLT in Eastern countries have been quite satisfactory, even compared to Western cadaveric transplantation. According to the survey by Furukawa in 2001, overall mortality rates in Eastern LDLTs average 19%, with 16% mortality in paediatric cases and 22% mortality in adult cases. Of course, this number could be affected by recipient preoperative status, and cannot be directly compared to other regions where LDLT is the only alternative to cadaveric transplantation, as indications for LDLT might differ.

The three primary causes of death comprised infection (3.3.9%), multiple organ failure (20.8%) and delayed graft function (10.9%). In the present survey, 11 cases (0.5%) of primary graft non-function (PNF) were observed, still a comparatively low rate compared with PNF in Western countries [13, 14].

With regard to morbidity, biliary complications represent the Achilles' heel of LDLT, displaying high incidence in both hepaticojejunostomy (Roux-en-Y fashion) and duct-to-duct anastomosis [15].

Donor morbidity and mortality
Donor safety must have the highest priority in LDLT. As yet, no donor deaths have been reported from Asia, although several have been encountered in Europe and the USA. Special consideration for donors is needed regarding general risks such as deep vein thrombosis leading to pulmonary embolism. Donor complications were identified in 13.8% of cases in the survey by Furukawa. The most common donor complication was bile leakage (28%), followed by wound infection (17%), hyperbilirubinemia (16%), gastrostasis (14%) and atelectasis (8%). Again, donor safety is a more important consideration than anything else in LDLT.

Kyoto experiences

Introduction
LDLT in Japan displays a slightly different position to that seen in other Asian countries. Japan is highly dependent on LDLT (99.2%), more so than any other Asian country. Only 14 liver transplantations from brain-dead donors have been undertaken in the entirety of Japanese transplant history, compared with 1789 LDLTs by 2001. This means that the chance of receiving a cadaveric donation is almost non-existent in Japan, and it is no exaggeration to say that LDLT represents the only option for treating end-stage liver disease.

Strategies for graft size matching
Our indications for LDLT were initially for small children, utilising left lateral segment graft in 1990. Since then, enthusiasm for and familiarity with this procedure has led to its adoption for larger patients. Following early experiences of auxiliary partial orthotopic living donor liver transplantation (APOLT) for metabolic diseases [16, 17], the technique was applied to larger recipients to overcome graft size mismatching [18]. However, the total positive impact was small, basically due to severe deterioration of liver function in patients. APOLT is now employed only in select cases, such as metabolic disorders.

Mention has already been made of the shift in graft selection - that is, from left-sided graft for paediatric cases to right-sided graft for adult recipients to mitigate graft size mismatching. Right lobe graft has seen regular use for larger recipients since 1998 [19], and numbers of adult patients now surpass those of children. Even though right lobe graft appears sufficient from the perspective of graft recipient body weight ratio, poor liver function is occasionally encountered, mainly attributable to congestion of the anterior segment of the liver graft. Therefore, after the V5/V8 reconstruction era [20], right lobe graft with MHV needs to be harvested in selected cases, following precise evaluation of anatomical variations with segmental volumetry to ensure donor safety.

On special occasions, the volume of liver graft is insufficient for adult recipients even with the use of the...
right lobe. As an alternative solution, right and left lateral lobe grafts from two donors have been employed [21].

In contrast to the above problems, some demand also exists for a solution to the problem of large-for-size LDLT grafts for small infants. Our current strategy has shifted from the use of only-skin closure or prosthesis interposition to the use of a monosegmental graft comprising segment 2 or 3. Monosegmental graft has been utilised in 12 children (recipient body weight range: 3.5-7.4 kg) with excellent results.

**ABO barrier**

In our programme, living donors are selected from close family members (third-degree relatives or legally/socially accepted spouse of patient). When available donors are confined to family members, the problem of ABO incompatibility is often encountered. Although results for ABO-incompatible LDLT in small children are excellent, the risks of uncontrollable humoral rejection are not negligible in larger children and adults, despite trials of various immunoregulatory agents (Figure 7a). To overcome the ABO barrier, the Keio University group has introduced a protocol for intraportal infusion of immunomodulators [22]. After adoption of this protocol by Kyoto University in November 2000, the regimen seems to have displayed promise, and modifications of the protocol still remain under investigation for optimal results (Figure 7b).

**Conclusion**

The East Asian history of LDLT is certainly quite different to that in other regions where cadaveric transplantations have long been accepted. LDLT is no longer a "necessary evil", but more of 'sharing-your-lives' between living donor and recipient. The conditions and mores of Eastern countries have created such demand for LDLT that further refinements are required, along with intellectual and technical exchange with Western countries regarding all types of liver transplantation.

**References**


8 Lo CM, Fan ST, Liu CL, *et al.* Adult-to-adult living donor