Review Article

Liver Transplantation in Asia: Past, Present and Future

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Abstract

With the technical advances and improvements in perioperative management and immunosuppressants, liver transplantation is the standard treatment for patients with end-stage liver diseases. In Asia, a shortage of deceased donor liver grafts is the universal problem to be faced with in all transplant centres. Many surgical innovations are then driven to counteract this problem. This review focuses on 3 issues that denote the development of liver transplantation in Asian countries. These include living donor liver transplantation (LDLT), split liver transplantation (SLT) and liver transplantation for hepatocellular carcinoma (HCC). Minimal graft weight, types of liver graft to donate and the inclusion of the middle hepatic vein with the graft are the main issues to be established in LDLT. The rapid growth and wide dissemination of LDLT has certainly alleviated the supply-and-demand problem of liver grafts in Asia. SLT is another attractive approach. Technical expertise, donor selection and graft allocation are the main determinants for its success. Liver transplantation plays a key role in the management of HCC in Asia. LDLT would be the main strategy in this aspect. The issue of extending the selection criteria for HCC patients for LDLT is still controversial. On the whole, future developments to increase the donor pool for the expanding recipient need in Asia would involve transplantation from non-heart beating donor and ABO incompatible transplantation.

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Introduction

Liver transplantation is the best treatment modality for patients with end-stage liver diseases. It has been landmarked as one of the most important advances in the medical field. Its applicability is expanding tremendously worldwide, particularly in many Asian countries. The history of liver transplantation dates back to 1963 when Starzl in Colorado first attempted cadaveric liver transplantation (CLT) in human in the world.[1] Following this failed trial, the first successful cadaveric liver transplantation was performed by Starzl again in 1967 and long-term survival result was then reported.[2] In Asia, this innovative operation was started early in 1964 by Nakayama in Japan, using a graft from a non-heart beating donor.[3] It was not until 1978 that the second CLT in Asia was performed by researchers in China for a patient with advanced HCC. Over 50 CLTs were then carried out in the early 1980s in China but there was no long-term survivor from these operations.[4] In Taiwan, Chen performed the first successful CLT with long-term survival in 1984.[5] Following the implementation of legislation on brain death in Asian countries (Taiwan, Japan, Hong Kong and Korea) from 1987 to 1999, the practice of CLT propagated in Asia.[6] In fact, the early success of CLT relied on the two major contributing factors, including the clinical use of calcineurin inhibitor (cyclosporine A)[7] and the improved graft preservation by hypothermic perfusion of University of Wisconsin solution.[8]

From the Worldwide Transplant Directory reported in the year 2000, only 417 of 9,354 liver transplants were from Asian countries.[9] Apart from sophisticated equipments, expensive drugs and extensive manpower involved in such a complex surgery, successful liver transplantations always require the supply of good-quality liver grafts. In fact, the relative slow progress of CLT in Asia as compared with Western countries was mainly due to the cultural and religious barrier of organ donation from the deceased in most Asian countries. Despite education and promotion campaigns, there was no significant increase in the number of deceased organ donation rate in Asia in

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the past 10 years. The number of deceased donors per million of population ranged from 0.07 to 6.5 among the Asian transplantation centres in the year 2005. Such deceased organ donation rates were far below those of Western countries (35.1 per million population in Spain and 25.2 per million population in the US).[10]

To overcome the critical shortage of deceased organ donation, surgical innovations of liver transplantation were driven in Asian countries, including living donor liver transplantation (LDLT) and split liver transplantation (SLT). These operations are technically more demanding and they involve complicated manpower and more logistical issues such as donor selection and safety. Besides, chronic viral hepatitis by hepatitis B and C viruses is prevalent in Asian countries and hepatocellular carcinoma (HCC) developed in the background of cirrhosis becomes the major cancer burden in Asia. The clinical impact of liver transplantation for HCC has changed the treatment strategy for HCC since both pathologies (viral hepatitis and liver cancer) can be cured in one goal ultimately. However, the exact role of liver transplantation for HCC is yet to be defined due to the mismatch between the organ donation rate and high incidence of HCC in Asia. This review will focus on each of these aspects that denote the relentless contributions from the East in the development of liver transplantation.

Living Donor Liver Transplantation

History of LDLT in Asia

The concept of LDLT originally started in Western countries. Smith proposed the idea of liver transplantation using a liver graft from a living donor in 1969.[11] The first attempt of LDLT was made by Raia et al[12] in Brazil in 1988 and the first successful LDLT from adult to child was performed by Strong et al[13] in Australia in 1989. In Asia, the first LDLT was performed by Nagasue et al[14] of Shimane University in Japan in 1989. Since then, this operation has been rapidly taken up and propagated among the Asian transplantation centres. Many technical refinements have taken placed to optimise its benefits for patients. Initial LDLT programmes involved transplanting left lateral section graft from a parent donor to a paediatric patient. To suit the demand of adult patients, frontiers of the Shinshu group in Japan has modified the operation by using extended left lobe graft and reported the first successful adult-to-adult LDLT using the left lobe in 1993.[15] The recipient suffered from primary biliary cirrhosis and the donor was her son. Even with the left lobe graft, the minimal graft volume for sustaining the patient's survival might not be reached if there was body size mismatch between the recipient and donor. In such instance, the use of right lobe graft could solve the problem of graft-to-body size mismatch. In 1993, Kyoto group reported a case of unplanned adult-to-child LDLT using right lobe to avoid the difficult arterial anatomy of the donor's left lobe.[16] Subsequently, the first successful adult-to-adult LDLT using right lobe graft including middle hepatic vein (MHV) was performed at Queen Mary Hospital in Hong Kong in 1996.[17] Further advances in the techniques of LDLT were then reported in other Asian centres, including the addition of caudate lobe to left lobe graft[18] and the use of right lateral sector graft[19] in Japan, and the dual grafts from 2 donors for 1 recipient[20] in Korea.

Minimal Graft Volume

Adequate graft size is essential to ensure satisfactory early graft function and recipient survival after LDLT. Graft-to-body size mismatch and the resulting small-for-size syndrome is still the major problem to be solved in adult-to-adult LDLT. The histopathological features of small-for-size graft injury include hepatocyte ballooning, steatosis, apoptosis, sinusoidal congestion, endothelial denudation and parenchymal cholestasis. Experimental study has demonstrated that the minimal graft weight for successful orthotopic liver transplantation was 25% of the original liver weight.[21] In a retrospective study on 276 patients with LDLT, Kiuchi et al[22] found that the use of small-for-size liver graft of less than 1% of the recipient body weight resulted in a significantly poor graft survival. This observation is related to the small-for-size graft injury and the reduced metabolic and synthetic capacity of the small-for-size liver graft. Using mathematic formulation, estimated standard liver volume (ESLV) of the recipient could be accurately derived.[23] The minimal requirement of a small-for-size graft for predictable recipient success was then set to range from 30% to 40% of ESLV.[24,25] Portal hyperperfusion and hence portal hypertension are the major contributing factors for hepatocyte damage in small-for-size graft. Various procedures have been reported to modulate superfluous portal vein flow in order to alleviate small-for-size graft damage. These included hemiportocaval shunt[26], mesocaval shunt[27], splenic artery ligation[28], splenectomy and pharmacological modulation.[29] The use of heat shock protein inducer has been shown to suppress inflammatory response and improve survival after massive hepatectomy in rat model, and this may become a new treatment strategy for the small-for-size liver graft.[30]

Venous Drainage of Anterior Section of Right Lobe Graft

LDLT using right lobe graft is the preferred procedure if there is donor-to-recipient body weight mismatch. The adequate graft size can be achieved with the use of right lobe liver graft. Nevertheless, the importance of good venous drainage of the right lobe liver graft remains the fundamental issue to ensure adequate graft function. The detrimental effects of impaired venous drainage of anterior

section (segment 5 and 8) of the right lobe graft include the venous congestion and hepatic necrosis of that part of the liver graft.[31] This is frequently observed when the MHV tributaries from the anterior section are ligated in case of not including MHV in the right lobe graft. The recipient may manifest small-for-size syndrome, and the risk of hepatic artery thrombosis increases due to poor hepatic venous outflow. The impaired graft regeneration is unavoidable due to the elevating sinusoidal pressure and disrupted sinusoidal endothelium.[32,33]

Different approaches are adopted in Asian transplantation centres to ensure venous drainage of the anterior section of the right lobe graft. Korean group advocated the application of "modified right lobe liver graft" by reconstruction of the hepatic venous drainage of the anterior section directly into the inferior vena cava, using interposition vein graft. Satisfactory survival outcome was reported by the same group using this modified graft.[34] The Tokyo group adopted the selective reconstruction of venous drainage of the anterior section based on the presence of dominant segment 5 and 8 hepatic veins by intraoperative ultrasonography and the perfusion of anterior section when the right hepatic artery and the MHV were clamped in the donor operation. The prominent segment 5 and 8 hepatic veins were anastomosed to the recipient MHV and left hepatic vein using interposition vein grafts in selected recipients.[35] The Kyoto group included MHV with the right lobe graft when the graft is MHV dominant, or the graft-to-recipient weight ratio of less than 1%, and the remnant donor left lobe volume of more than 35% in all cases.[36] The Taiwan group also used similar criteria to include MHV with the right lobe graft when the graft weight was less than 50% of ESLV of recipient, or the graft is MHV dominant.[37] It has been demonstrated by the Hong Kong group that routine inclusion of MHV with the right lobe graft resulted in uniformly good venous drainage of liver graft and thus favourable operative outcome was achieved.[38,39] This approach was considered to be crucial for patients with high metabolic demands and poor functional reserve, such as patients with fulminant hepatic failure or acute decompensation of chronic liver disease. In addition, the Hong Kong group proposed the technique of hepatic venoplasty by joining MHV to the right hepatic vein of liver graft to form a single cuff on the back-table to further enhance the outflow capacity of liver graft.[40] With this approach of routine inclusion of MHV with the right lobe graft, special care was necessary to preserve segment 4b hepatic vein with donor liver remnant to safeguard donor safety.[41] There was some concern about the donor safety by harvesting MHV with right lobe liver graft. Up till now, there is insufficient evidence supporting the direct relationship between donor morbidity and the absence of MHV in donor liver remnant. Donor safety in terms of low mobidity and early liver remnant regeneration after right hepatectomy with inclusion of MHV has been reported.[42]

Biliary Reconstruction

The incidence of biliary complication remains high (up to 67%) after LDLT.[43-45] This complication has significantly affected the quality of life of LDLT recipients and occasionally causes graft and patient loss. The ischaemia of the right hepatic duct and the high incidence of anatomical variation of right duct system may account for this high complication rate. To avoid ischaemia of the right hepatic duct, it is mandatory to preserve the blood supply of the bile duct. Understanding the arterial supply of the right hepatic duct from the right hepatic artery and the hilar plate, it is necessary to avoid dissection into the area between the right hepatic duct and the right hepatic artery beyond the point of the right hepatic duct division in the donor operation.[46] In addition, sufficient liver tissue around the right hepatic duct should be preserved to ensure adequate venous drainage for the right hepatic duct. High-quality cholangiogram by fluoroscopy helps to delineate complicated right hepatic ductal system if anatomical variation exists. By obtaining right anterior oblique view, the right anterior and posterior hepatic ducts can be clearly defined.[47]

Hepaticojejunostomy (HJ) was the preferred biliary reconstruction technique in the early series of LDLT.[48] However, it was associated with long operating time, contamination of operation field due to opening of small bowel, and delayed in return of gastrointestinal function. In contrast, duct-to-duct reconstruction has the advantages of avoidance of contamination of operation field and early return of bowel function. Since the function of sphincter of Oddi is preserved in duct-to-duct reconstruction, enteric reflux to biliary system and the resulting ascending infection can be potentially avoided. In addition, this reconstruction technique allows the subsequent intervention by endoscopic retrograde cholangiopancreatography if necessary. The feasibility of duct-to-duct biliary reconstruction has been reported and there was no proven difference in the incidence of biliary complication between HJ and duct-to-duct reconstruction from retrospective studies. In a study by Liu et al,[45] the outcomes of 41 LDLT recipients who underwent duct-to-duct reconstruction were compared with those of 71 LDLT recipients who underwent HJ. There was no significant difference in biliary complication between the duct-to-duct group (24%) and HJ group (31%). In an attempt to lower biliary complication following duct-to-duct reconstruction, Ishiko et al[44] advocated the practice of continuous suture combined with external stent. Possible factors reported to be associated with increased risk of biliary complication after duct-to-duct reconstruction included multiple ductal openings and high preoperative

Model for Endstage Liver Disease (MELD) score (≥35).[45] Whether continuous or interrupted sutures, and stent or no stent make any significant difference in preventing biliary complication requires a higher level of clinical evidence by randomised controlled trials to validate.

Right Lateral-section Graft and Dual Grafts

LDLT using right lobe graft has imposed a potentially higher surgical risk on the donors, who may have a relatively small liver remnant. The Hong Kong group has suggested that a liver remnant of at least 30% should be preserved to ensure donor safety.[49] To accommodate this safety limit, right lateral-section graft and dual grafts from 2 donors have been developed as the variant grafts for LDLT.

The utilisation of right lateral-section graft (segment 6 and 7) in LDLT was first advocated by the Tokyo group.[19] This variant graft was chosen under the conditions that donor left lobe volume was less than 30% of the estimated total liver volume, and the estimated volume of right lateral-section graft being larger than that of donor left lobe. The successful use of right lateral-section graft has been reported in 6 recipients by the same group.[50] However, the harvesting of this kind of liver graft was highly technically demanding and the associated bile leakage rate was reported as high as 50%. Hence, this variant graft has not been widely adopted in other transplant centres.

Lee et al[20] invented the use of dual liver grafts from 2 donors for LDLT. The usual grafts chosen were left liver or left lateral section. The implantation of this variant graft was complex. The first graft was implanted orthotopically, while the second graft was rotated 180^0 and implanted heterotopically in the right upper quadrant of the recipient. Technical modification was required for the implantation of the second graft, in which biliary reconstruction was performed prior to the anastomoses of portal vein and hepatic artery. This dual graft technique carried unwelcome ethical issues concerning 2 major operations in 2 healthy donors, with the associated potential morbidities and mortalities for 1 recipient. Again, this variant liver graft is not widely performed in the world.

Donor Safety

Donor safety is crucial in the application and expansion of LDLT. Never in the history of surgery does a healthy person undergo a major operation like hepatectomy. The balance between recipient success and donor risk should always be considered when LDLT comes into clinical practice. In one survey of 1,508 living liver donors receiving hepatectomy in 5 Asian transplantation centres from 1990 to 2001, the overall donor complication rate was 15.8%, and 1.1% of donors required re-operation.[51] The complication rate of right lobe donor was higher than that of left lobe donor (28% vs. 7.5%). In particular, right lobe donors had experienced more serious complications, such as cholestasis, bile leakage, biliary stricture, portal vein thrombosis, intra-abdominal bleeding and pulmonary embolism. There was no hospital mortality but 1 late donor death was reported 3 years after operation. The cause of that donor death was unknown. The Hong Kong group has reported another late donor death which occurred 10 weeks after surgery as a result of duodenocaval fistula formation from an acute duodenal ulcer. The overall donor mortality was 0.5%.[42] In Japan, the first donor mortality occurred in a hypertensive lady who died from liver failure after right liver donation with a residual left liver of 28% of the total liver volume.[52] With more than 12,000 living donor operation performed worldwide, the mortality rates for right liver donor and left liver donor approached 0.5% and 0.1%, respectively.[53] There are 2 recent large Asian series reporting the living donor outcome. Umeshita et al[54] have evaluated 1,853 donors in 46 liver transplant centres in Japan. Postoperative complications occurred in 12% of donors and the complication rate was significantly higher in right liver donors than left liver donors. In another study of 1,162 living donors by Hwang et al[55] from Korea, there was no donor mortality and 3.2% donors experienced major complication. The donor complication rate could be reduced to 1.3% when donor liver remnant exceeded 35%, except for young donors with no hepatic steatosis. Hence, careful donor selection and meticulous donor operation by experienced transplant surgeons should be vigilantly adhered to in order to maintain or decrease donor mortality and morbidity.

Ethical Issues

The number of LDLT has grown exponentially out of that of CLT in Asia, because of the scarce supply of liver grafts in the deceased donor pool. From an international survey on liver transplantation in Asia conducted in 2006,[10] the number of CLT in Asia has remained static (80 to 140 cases per year) over the past decade. Meanwhile, there was resurgence in the number of LDLT since the 1990s when LDLT using right liver was introduced. The annual number has increased from less than 50 cases in 1999 to 1,387 cases in 2005. The proportion of patients receiving LDLT exceeded 90% among patients who had undergone liver transplantation in the year 2005. With such high proportion of LDLT in Asian transplant centres, ethical justification for using living donor liver grafts for transplantation should be clearly established. The risk-benefit ratio of both the donor and recipient should be well balanced, and not underestimated. Patient selection in terms of recipient and donor selection plays a crucial role in the ethical justification of LDLT. The expected recipient benefits, potential donor risks (see above) and recipient risks ought to be assessed in great details in both medical and psychological grounds. In

general, living organ donation must be absolutely voluntary, with consent given on the basis of unbiased information and chosen only when the option for CLT is practically nil.[6] Only if the donor operation can be performed with minimal risk by experienced surgeons, the indications are clear, and the living donor gives voluntary informed consent, LDLT is justified.

Split Liver Transplantation

The idea of bipartition of a whole deceased liver graft for use in 2 recipients helps to counteract the prevailing problem of organ shortage for CLT. The success of SLT depends very much on the proper selection of deceased liver graft to split. There is a tendency to reserve SLT for deceased donor younger than 50 years old and for those with stable haemodynamics.[56] It is generally believed that deceased graft of young age is more tolerable to tissue injury due to ischaemic-reperfusion injury and manipulation during the splitting procedure. In the classical design of SLT, the deceased liver was split into the left lateral section and the right liver together with segment 4 and caudate lobe. In such a strategy, a deceased liver graft can suit a small child and an adult, or a bigger child, respectively. Theoretically, the application of SLT can be expanded to split a deceased graft for 2 adult recipients. This strategy would certainly shorten the waiting time for potential recipients on the waiting list. *In situ* and *ex situ* splitting are the 2 splitting methods in SLT. *Ex situ* splitting is performed at the back table after conventional procurement procedure. Since it is carried out in a virtually bloodless graft, vital structures are more difficult to identify and secure haemostasis on the liver cut surface is difficult to ensure. Because of long benching time, the duration of cold ischaemia of the deceased graft is prolonged. In contrast, *in-situ* splitting is conceived to facilitate precise dissection of vital structures. The haemostasis of liver cut surface can be secured and cold ischaemic time is shortened. This technique involves splitting the liver in the heartbeating donor, followed by the conventional procurement procedures. It requires a haemodynamically stable donor and longer operating time for organ procurement.

The history of SLT in Asia started in 1997 when the Taiwan group performed the first SLT in Asia using *ex-vivo* splitting technique.[57] Subsequent SLTs were performed in 5 transplantation centres in Singapore, Korea, Japan and Hong Kong. Until 2000, a total of 26 SLTs have been performed in Asian transplantation centres.[58] An emerging graft source for SLT is the liver graft from a patient with familial amyloid polyneuropathy (FAP). FAP has a delayed onset of symptoms related to the accumulation of amyloid deposition in various organs, including the heart and gastrointestinal tract. Liver graft from FAP is ideal for splitting since it is functionally and anatomically normal. In practice, 1 deceased or living donor for a patient with FAP can benefit 3 recipients on the transplant waiting list under this strategy (Domino liver transplantation). The first SLT from a patient with FAP in Asia was performed by the Kyoto group in 1999 and the split hemiliver grafts were transplanted to 2 adults who weighed 50 kg each.[58] Biliary leakage was the most common reported complication in the Asian series. Other complications included hepatic artery insufficiency, portal vein thrombosis, intra-abdominal hemorrhage and gastrointestinal bleeding. The reported mortality rate was 11%.[58]

Liver Transplantation for Hepatocellular Carcinoma

Patient Selection and Prioritisation

HCC is the fifth most common and the third most deadly cancer in the world.[59] The close association between HCC and the underlying chronic liver disease due to viral hepatitis infection renders this tumour difficult to be cured by hepatic resection or loco-regional therapies. Liver transplantation is an attractive treatment option that offers a chance of curing both tumour and underlying cirrhosis. Nevertheless, early studies in the West have demonstrated that poor outcome after liver transplantation for HCC was related to high pathological tumour-node-metastasis staging.[60] Vascular invasion by tumour was regarded as the most important poor prognostic factor. Hence, tumour size and number of tumours were then used as the surrogate parameters for the likelihood of vascular invasion by tumour. With careful patient selection, favourable survival outcome could be obtained after liver transplantation for HCC using the 2 widely adopted selection criteria, namely the Milan criteria[61] and the University College of San Francisco (UCSF) criteria.[62]

Although liver transplantation is a well established treatment modality for HCC in the West, its applicability in the management of HCC patients in Asia is entirely different. The mismatch between organ donation and high incidence of HCC in Asia mandates a strict system of organ allocation. The patient priority on the waiting list is primarily determined by liver disease severity based on the MELD score.[63] Unlikely the organ allocation system in the US which assigns additional score at regular intervals to HCC patients, there is no prioritisation of HCC patients for organ allocation in Asia to avoid the fact that the limited deceased donor graft would inevitably be given to the large number of HCC patients. Hence, tumour progression to the extent beyond the transplantation criteria due to the prolonged waiting period is a great concern in Asian centres. In order to minimise the drop-out rate from the waiting list, various approaches are adopted, including bridging treatment for HCC, salvage transplantation after prior hepatectomy and LDLT for HCC.

Bridging Therapies for HCC

Significant drop-out rate from the waiting list because of tumour progression has greatly reduced the overall survival of HCC patients waiting for transplantation.[64] Bridging therapies to halt or delay tumour progression include local ablation techniques and transarterial chemoembolisation. The induction of tumour necrosis by these treatments may additionally reduce tumour dissemination during transplantation and prevent recurrence. The efficacy of these bridging therapies has been demonstrated in the Western series. Mazzaferro et al[65] have reported the efficacy of radiofrequency ablation in 50 HCC patients waiting for transplantation. The drop-out rate was 0% with a median waiting time for transplantation of 9.5 months. The 3-year post-transplantation overall survival rate was 83%. In another study by Graziadei et al,[66] 47 patients with HCC within the Milan criteria were treated by transarterial chemoembolisation before transplantation. The 5-year overall survival was 94% by intention-to-treat analysis. Despite the encouraging results of these studies, strong evidence in the form of well-designed randomised controlled trial is still lacking to support the efficacy of such treatments. Nonetheless, these pre-transplant treatments may confer some selection effect on tumours with favourable biological behaviour and it is the tumour response to pre-transplant treatments that has major impact on patient survival after transplantation.[67]

Salvage Transplantation

It is plausible in HCC patients with well-preserved liver function that primary hepatectomy can be safely performed and salvage transplantation is reserved for recurrence or hepatic decompensation after initial operation. This approach would certainly reduce the number of HCC patients to be recruited into the waiting list since those HCC patients are rendered tumour-free after hepatectomy and there is a time lag between primary hepatectomy and tumour recurrence or liver decompensation. The debate on the choice of primary transplantation versus primary hepatectomy followed by salvage transplantation is still ongoing. There have been conflicting results from 2 French groups on the comparison of primary and salvage transplantation. Belghiti et al[68] compared 18 patients who underwent salvage transplantation following primary hepatectomy with 70 patients undergoing primary transplantation for HCC. The outcomes of 2 strategies were comparable. However, Adam et al[69] reported that salvage transplantation was associated with a higher operative mortality, an increased risk of recurrence and a poorer outcome compared with primary transplantation for HCC. In Asia, Hwang et al[70] have shown that overall survival rate after salvage transplantation was similar to that after primary transplantation, particularly when the extent of recurrent tumour was within the Milan criteria. The Hong Kong group has found a selection bias for LDLT as salvage transplantation for recurrent HCC, which was an independent predictive factor for recurrence.[71] Nonetheless, the critical problem of organ shortage in Asia favours the option of primary hepatectomy followed by salvage transplantation. In other words, the pressure on the waiting list would inevitably be reduced by this strategy.

Living Donor Liver Transplantation for HCC

LDLT can theoretically provide an unlimited source of liver grafts for HCC patients whose tumour status is within the selection criteria. The uncertainty of prolonged waiting time on the list and the risk of drop-out can virtually be eliminated by LDLT. There were 2 decision analyses that have supported the application of LDLT for HCC. These hypothetical studies concluded that LDLT is superior to CLT for patients with HCC within the Milan criteria when waiting time for deceased liver graft exceeds 6 months.[72,73] The unaffected donor pool of organs for patients with non-malignant liver disease is another crucial advantage of LDLT since the living donor graft is a dedicated gift directed exclusively to the recipient. The role of LDLT and its intention-to-treat survival benefit over CLT in patients with early HCC has been demonstrated by the Hong Kong group. Lo et al[74] found that patients who opted for LDLT had significantly better survival outcomes when compared with those who waited for CLT.

Caution should be taken when assuming the superiority of LDLT over CLT in some aspects. First, donor voluntarism and donor selection criteria form the main frame determining the availability of living donor liver graft. The Hong Kong group has reported that >50% of patients with transplantable HCC might not have suitable voluntary donors.[74] Second, there is a tendency toward a higher rate of tumour recurrence following LDLT, when compared with CLT for HCC. A multi-centre LDLT cohort study (A2ALL) from the West has reported a significantly higher 3-year tumour recurrence rate after LDLT (29%) compared with that after CLT (0%).[75] Similar results were obtained from the Hong Kong group.[71] Some of the possible contributing factors for the high tumour recurrence after LDLT are selection bias for patients with aggressive tumour behaviour, elimination of natural selection during waiting period, and enhancement of tumour growth and invasiveness by small-for-size graft injury and regeneration.[33,76]

Extending the tumour selection criteria to include patients with more advanced HCC to receive LDLT is an attractive option, since a living donor graft is not subject to the system of equitable allocation. The Kyoto group has adopted the extended criteria that included any size or numbers of tumours provided there was no gross vascular involvement or distant metastasis. The reported 4-year overall patient

survival was 64% in all HCC patients and 59% in patients whose tumours were beyond the Milan criteria.[77] In another study from 49 transplantation centres in Japan on 316 HCC patients receiving LDLT, the Milan criteria was adopted in one third of the transplantation programmes. The overall survival and recurrence-free survival at 3 years were significantly worse when the Milan criteria were not met (60.4% vs. 78.7% and 52.6% vs. 79.1%). The preoperative alpha feto-protein level, tumour size, vascular invasion and bilobar distribution were identified as independent risk factors for recurrence after LDLT.[78] Similar results were also reported by Hwang et al[79] based on 4 transplantation programmes in Korea. Hence, the policy of extended criteria of liver transplantation for HCC is yet to be further validated by a large-scale study.

Predictors of Vascular Tumour Invasion

The finding that recurrence of HCC in liver graft and distant organ after liver transplantation strongly suggests the presence of circulating cancer cells in pre-transplantation state as a result of microvascular tumour invasion in HCC patients. Recent advance of molecular biological techniques allow the detection of occult circulating cancer cells. Reverse transcription and amplification of messenger RNA (mRNA) of specific markers (albumin and alpha-fetoprotein) has been applied in this context.[80,81] The detection of albumin mRNA has low specificity for circulating cancer cells since it is present in the majority of healthy controls. In contrast, the presence of alpha feto-protein (AFP) mRNA-expressing cell in peripheral blood may be a useful indicator of recurrence after liver transplantation for HCC.[82-84] Efforts have been made to validate the specificity of this molecular marker for predicting vascular invasion by HCC. Another useful marker is serum des-g-carboxy prothrombin (DCP) and its application as a predictor of microvascular tumour invasion has been suggested by Shirabe et al.[84]

Future Prospects of Liver Transplantation in Asia

Non-heart-beating Donors

It is the usual practice in most Asian transplantation centres that cadaveric liver grafts are procured from brain-death donors under the regulation of transplantation legislation. Liver grafts from non-heart-beating donors (NHBD) are therefore considered as a potential for expanding donor pool in liver transplantation in Asia. The first liver transplantation from a NHBD was performed by Nakayama in Japan in 1964.[85] The major drawback of the use of liver graft from NHBD instead of a brain death donor is prolonged warm ischaemic time. In NHBD liver graft, the effects of warm ischaemia are superimposed on the injury of cold ischaemia. The warm ischaemia causes injuries to the hepatocytes, whereas cold ischaemia leads to injury to sinusoidal endothelial cells.[86] In addition, warm ischaemia in NHBD graft may increase the incidence of ischaemic biliary stricture. Despite these disadvantages associated with a NHBD liver graft, CLT using this type of liver graft has being increasingly used in the West with acceptable survival results. From survival analysis using the United Network for Organ Sharing (UNOS) database, it has been shown that 3-year patient survival was inferior in the NHBD group compared with the brain death donor group (63.3% vs. 72.1%). Moreover, the primary non-function rate after transplantation was significantly higher in the NHBD group than in the brain death group (11.8% vs. 6.4%).[87] Future developments on the use of this type of liver graft should focus on the new strategies in organ preservation to minimise warm ischaemia, such as normothermic recirculation, normothermic preservation and cytoprotection. Currently, the NHBD liver graft is utilised with great caution in the West under strict guidelines: donor age <60, stable hemodynamic status of recipient, warm ischaemia <30 minutes, cold ischaemia <8 hours and discarding organ with significant steatosis.[87,88] In Asia, another hurdle to cross is the general acceptance on the donation of controlled NHBD grafts due to the inherited conservative views and cultural beliefs of the general population. Education and promotion campaigns on this issue are therefore mandatory in Asian countries.

ABO Blood-type Incompatible Liver Transplantation

With the popularity of LDLT in Asian countries, the relationship between donor and recipient is often living-related. Herein, the problem of an ABO blood-type incompatibility between voluntary donor and recipient is unavoidable. The critical complication lies on the occurrence of hyperacute rejection, which is mediated by the pre-existing antibody against donor blood-type antigen. The graft survival will be significantly reduced due to the early hepatic necrosis and later intractable bile duct damage.[89-91] The experience of ABO incompatible live transplantation is mainly obtained from the West. The overall survival in ABO incompatible LDLT was significantly lower than that of blood-type compatible LDLT.[92] In children <3 years old whose immune function is not well established, ABO incompatible liver transplantation has been more successful.[93] Recently, promising results of ABO incompatible liver transplantation has been reported using A_2 donors, which is a subgroup of blood-type A and is less reactive.[94] Potent immunosuppression using antithymocyte globulin, interleukin-2-receptor antagonist and anti-CD20 antibody, and perioperative plasmapheresis may help to reduce immuno-mediated graft damage in ABO incompatible transplantation. The Japan group reported the use of intraportal infusion therapy using prostaglandin

and steroid to prevent serious complication in this type of transplantation. The reported 5-year survival was improved up to 51.2%.[95] Later, the Kyoto group modified the technique by adopting hepatic artery infusion and reported further improvement in the survival result.[96] Since ABO incompatible liver transplantation may be the only option if there is no ABO compatible donor in LDLT, future studies are needed to establish optimal peri-transplantation management to minimise the graft damage in this type of transplantation.

Education and Promotion of Organ Donation

In reality, the demand for organ transplantation has rapidly increased all over the world due to the increased incidence of vital organ failure and the great improvement of transplantation outcome. The organ shortage has deprived thousands of patients a good quality of life and has increased the financial burden in the cost of medical care of those patients. The implementation of appropriate educational programmes for the public regarding the need and benefits of organ donation can provide an efficient way to alleviate this crisis of organ shortage. The educational process can be carried out through the media, schools, colleges and appropriate training programmes for medical staff. With the current popularity of the internet and multimedia communication, such messages can be widely distributed. To pursue these programmes efficiently, government funding or donation from charity is equally necessary. It is only when the awareness of the public on the issue of organ shortage increases that the maximal benefits of liver transplantation can be delivered to patients who are on the edge of the cliff.

Conclusion

Shortage of deceased organs is a universal problem in the field of liver transplantation among all centres in Asia. LDLT has been widely practiced in Asia to counteract this problem. Balancing the recipient benefits and donor risks should be vigilantly considered in LDLT. Issues of minimal graft weight, side of liver to donate and inclusion of the MHV with graft or donor are still debatable and associated technical innovations and refinements are ongoing. SLT is another approach to increase graft supply from limited deceased organ donation. It should be seriously considered among Asian centres. Technical expertise in splitting techniques, donor selection and graft allocation are the main determining factors for its success. Due to the high incidence of viral hepatitis, HCC is a growing indication for liver transplantation in Asia. LDLT would act as the dominant strategy in this aspect. For HCC patients with preserved liver function, primary hepatectomy and salvage transplantation for recurrence is an attractive approach. Whether to extend selection criteria based on the autonomy of the decision of donor and recipient in LDLT is still poorly defined. To further increase the donor pool for the lengthening recipient waiting list in Asian centres, liver transplantation using NHBD or ABO incompatible donor need to be further explored. Last but not least, education and promotion of organ donation in Asia is of paramount importance to alleviate the organ shortage crisis.

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