Liver Transplantation for Hepatocellular Carcinoma in Asia

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the selection criteria of patients with hepatocellular carcinoma for liver transplantation.
2. Describe the problems associated with the application of liver transplantation for hepatocellular carcinoma and the possible solutions.
3. Discuss the current status of liver transplantation for hepatocellular carcinoma in Asia.

ABSTRACT

Hepatocellular carcinoma (HCC) is a leading cause of cancer death, particularly in Asia where the major etiology, chronic hepatitis B virus infection, is endemic. The tumor frequently develops in a background of cirrhosis, and liver transplantation offers a chance to cure both the tumor and the underlying cirrhosis. The Milan criteria based on tumor size and number as an estimate of tumor burden are conventionally the gold standard in determining eligibility for transplantation, and the outcome is excellent. The shortage of organs from deceased donors has curtailed the adoption of extended criteria and led to the problems of long waiting times and dropouts. Several measures have been taken to tackle these issues, including prioritization of patients with HCC, use of pretransplant adjuvant treatment to prevent tumor progression, and living donor liver transplantation (LDLT). With a high incidence of HCC and a low organ donation rate, Asia has developed a distinctive pattern of indication and strategy in the application of liver transplantation. Over the last decade, the number of liver transplants in Asia has increased rapidly, by 10-fold, largely as a result of the development of LDLT. The proportion of patients who undergo liver transplantation for HCC is increasing and HCC comprises one third of the indication for liver transplantation in Asia. LDLT is the dominant strategy, accounting for 96% of the liver transplants for HCC. Many transplant programs accept patients beyond the Milan criteria, and the reported 3-year survival rate is about 60%. With the promotion of organ donation, better quantification of the benefit of LDLT for extended indications, and identification of predictors for survival, the practice of liver transplantation for HCC in Asia will continue to evolve. The Oncologist 2007;12:1321–1331

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INTRODUCTION
Hepatocellular carcinoma (HCC) is the fifth most common and the third most deadly cancer worldwide [1]. More than half a million cases are identified and about a similar number die of the disease each year [2]. HCC is closely associated with chronic liver disease and as many as 80% of cases occur in cirrhotic livers [3]. Although liver resection and local ablation are regarded as potentially curative treatments, the limited functional reserve of the liver restricts their application and there is a high chance of recurrence in the liver remnant [4]. Liver transplantation is the only treatment that offers a chance of cure for the tumor and the underlying cirrhosis by complete extirpation of both. The outcome of liver transplantation for early HCC in Western countries is encouraging, but the limitation of organ supply remains the main issue. With a much higher incidence of disease and a more critical shortage of organs in Asia, the barrier against liver transplantation for HCC seems insurmountable. In this article we review the literature on liver transplantation for HCC and the history of the development of liver transplantation in Asia focusing on the problems and solutions. Finally, we summarize the current practice and outcome of liver transplantation for HCC in Asia based on the results of a survey.

HEPATOCELLULAR CARCINOMA IN ASIA
Hepatitis B and C viruses are the most common etiologic agents for HCC [5]. Since hepatitis B virus (HBV) is more prevalent, >80% of HCC occurs in areas where hepatitis B is endemic, and the geographic distribution of HCC largely follows that of HBV [2]. Chronic HBV infection is endemic in Asia, where an estimated 300 million individuals infected with HBV live, representing about 75% of the world’s chronic HBV carriers [6]. The incidence of HCC in Asia is therefore high, particularly in eastern and southeastern Asia. China has the highest age-adjusted incidence of HCC (37.9 per 100,000 in males and 14.2 per 100,000 in females), and accounts for >50% of the cases in the world [1, 2]. Whereas the main etiology of HCC in most parts of Asia is hepatitis B, Japan is an exception [7]. As in Europe and the U.S., hepatitis C is more prevalent than hepatitis B in Japan [5], and hepatitis C virus–related HCC accounts for about 90% of HCC in that country [7].

The prognosis of HCC is poor. Hepatic resection as a potentially curative treatment is not feasible in >80% of patients at the time of diagnosis because of advanced or multifocal disease or inadequate functional reserve [8]. The natural history of untreated nonsurgical HCC in Asia is worse than for similar cases in Western countries. Based on patients included in the control arm of randomized control trials on nonsurgical therapy, the 1-year and 2-year survival rates of patients with untreated HCC were 7.8% and 0.9%, respectively, in a study from Hong Kong [9], and 54% and 40%, respectively, in a comparable study from Spain [10]. This disparity could be related to different thresholds for curative and palliative treatments. While cirrhosis, large tumors, and multiple lesions are regarded as contraindications for hepatic resection in the West, they are not in most hepatobiliary centers in Asia, thus leaving only very advanced tumors as nonsurgical [9]. Nonetheless, the difference in survival persists even when compared stage for stage (median survival for Okuda stage I and II disease of 31.9 months and 6.1 months, respectively, in Europe versus 5.1 months and 2.7 months, respectively, in Asia) [9, 10], suggesting a genuine difference in tumor behavior between HCC in the East and West that may be related to the difference in underlying etiologies.

LIVER TRANSPLANTATION FOR HCC
Liver transplantation may be the best curative treatment for HCC. First, it removes the tumor with the widest margin together with any intrahepatic metastasis. Second, it cures the underlying cirrhosis that is responsible for both hepatic decompensation and metachronous tumor after partial hepatectomy. Finally, it allows the histologic examination of the entire liver explant for the most accurate pathologic staging. The early results that focused primarily on patients with advanced HCC were, however, poor because of frequent tumor recurrence [11–14]. Over the last decade, there has been considerable improvement in the outcome of liver transplantation for HCC, which is attributed almost entirely to better patient selection rather than better surgery or adjuvant therapy.

Prognostic Indicators and Selection Criteria
Identification of the prognostic factors for survival has been a major focus of research. Histologic parameters such as vascular invasion and tumor differentiation are the most important indicators of biologic behavior in predicting recurrence [15–17]. Nonetheless, these features can only be determined preoperatively with a liver biopsy, which is associated with definite risks and may not yield consistent results. In particular, vascular invasion may not be easy to diagnose in a small biopsy specimen.

Tumor size and number, which can be determined by preoperative imaging as an estimate of tumor burden or stage, are useful surrogate markers of biologic behavior. Tumor size predicts both the likelihood of vascular invasion and tumor grade [18], but the relationship is nonlinear and a significant proportion of small tumors have unfavorable histology, whereas some larger ones do not [18]. In addition, the accuracy and objectivity of radiologic imaging re-
main a concern, and both under- and overstaging are not uncommon [19–22]. Nonetheless, because radiologic imaging is readily available, if necessary, repeatedly before transplant, radiologic parameters based on tumor size and number are still regarded as the best selection criteria for patients with HCC to undergo liver transplant in clinical practice.

The objective of the selection criteria for HCC is to set a transplantable limit in order to achieve a survival duration comparable with that of other patients with benign liver disease receiving transplants, so as to justify or prioritize the allocation of a liver graft. For >10 years since the landmark study by Mazzaferro et al. [23] in 1996, the Milan criteria have remained the gold standard. By restricting transplantation to patients with a solitary tumor up to 5 cm in diameter or with two to three tumor nodules each up to 3 cm in the absence of extrahepatic disease, 4-year overall and disease-free survival rates of 75% and 83%, respectively, can be achieved. Extended criteria, such as the University of California at San Francisco (UCSF) criteria, have been proposed to expand the tumor number–size limits to solitary tumor up to 6.5 cm or a maximum of 3 tumor nodules each up to 4.5 cm, and a total tumor diameter not exceeding 8 cm, without compromising patient survival [24].

The traditional pathologic tumor–node–metastasis staging system has poor predictive value for outcome after liver transplantation [23, 25, 26], and the University of Pittsburgh group [26] has therefore modified the criteria by including specific tumor characteristics, such as lobar distribution (unilobar or bilobar) and type of vascular invasion (microscopic or macroscopic), into a staging classification with better prognostic value [26]. The main drawback of the Pittsburgh criteria that limited its clinical application in practice was the need for information on vascular invasion, which is difficult to ascertain preoperatively without examining the liver explant. The Milan and UCSF criteria are currently the most popular reference criteria in deciding the candidacy of patients with HCC for liver transplantation.

Graft Allocation, Waiting Time, and Dropout
The limited availability of liver grafts not only restricts candidacy but also mandates a system of organ allocation according to priority. The prolonged waiting period frequently results in tumor progression to an extent beyond the transplantable criteria, leading to a patient’s removal or dropout from the waiting list [27, 28]. Hence, intention-to-treat analysis is more appropriate. In a study from Spain, where the organ donation rate is the highest in the world and the average waiting time is <6 months, 23% of patients who met the Milan criteria dropped out and the 2-year intention-to-treat survival rate was only 54% [27]. In another study from the U.S., the cumulative probabilities of dropout at 6, 12, and 24 months were 7.3%, 25.3%, and 43.6%, respectively [28]. As a result of the high dropout rate for patients with HCC, the Organ Procurement and Transplantation Network (OPTN) of the U.S. has reconsidered the priority of liver graft allocation. While waiting list priority was determined primarily by liver disease severity based on the Model for End-Stage Liver Disease (MELD) score [29], patients with HCC that fulfilled the Milan criteria were registered with an adjusted score and were subsequently assigned additional scores at regular intervals to reflect their risk for dropout as a result of tumor progression. With such priority listing, the access to timely liver transplant for patients with HCC has improved in the U.S. [30].

Despite a much higher dropout rate for patients with HCC on the waiting list in Asia, prioritization of patients with HCC for organ allocation is never an option because the large number of patients with HCC will inevitably take up most, if not all, of the very few available deceased donor liver grafts.

Pretransplant Treatment
Pretransplant neoadjuvant therapy in the form of percutaneous ablation or transarterial chemoembolization is applied to patients with HCC on the waiting list for different reasons. First, downstaging of advanced tumor may allow expansion of the current criteria without adversely affecting survival. Second, induction of tumor necrosis may reduce tumor dissemination during surgery and prevent recurrence. Finally, most transplant programs administer adjuvant treatment to patients on the waiting list to reduce tumor growth and hence avoid dropout. These adjuvant therapies have been tested only in the setting of observational studies, and there are still no evidence-based data in strong support of the efficacy of such treatments administered for various reasons [31–33]. Most transplant programs, however, are reluctant to simply observe patients with HCC on the waiting list, and feel obliged to offer neoadjuvant therapy in order to prevent tumor progression. While such treatment is not meant as neoadjuvant therapy a priori and its impact on dropout rates has not been ascertained, it may confer some selection effect for tumors with better biological behavior, and it is the response to pretransplant therapy that has an impact on post-transplant survival [34–36].

Salvage Transplantation
Liver transplantation is widely accepted as the best treatment for early HCC in patients with decompensated cirrhosis of Child B and C grade. For patients with normal liver or Child A cirrhosis who can tolerate partial hepatectomy, the
choice of primary transplant versus salvage transplant only for recurrence or hepatic decompensation after liver resection is debatable. The survival rate of partial hepatectomy for early transplantable HCC is comparable with that of transplantation, but the recurrence-free survival rate is lower [37, 38] because of the high incidence of intrahepatic recurrence resulting from intrahepatic metastases or metachronous hepatocarcinogenesis in the cirrhotic liver remnant. Hence, primary transplantation may have an advantage. Nonetheless, salvage transplantation is feasible in many of these patients because the intrahepatic recurrences frequently remain transplantable [39]. The outcome of primary versus salvage transplant is controversial, with two French groups reporting contradicting results. Belghiti et al. [40] found that the outcomes of the two strategies were comparable, while Adam at al. [41] claimed contrasting results, with a higher operative mortality and greater risk for recurrence after salvage transplantation. Experiences in Asia with salvage transplant using living donor liver grafts are also conflicting. Hwang et al. [42] from Korea showed that the outcome of 17 salvage living donor liver transplants (LDLTs) was not inferior, but a report from Hong Kong demonstrated a selection bias for LDLT as salvage transplant, which was an independent predictive factor for recurrence [43]. Although there is still doubt as to the claim that salvage transplant can be done with an outcome similar to that of primary transplant, the issue of organ shortage favors the adoption of primary resection followed by salvage transplantation as the preferred strategy in most centers because primary transplantation is not immediately available, is associated with dropouts, and intensifies the pressure on the waiting list. This is particularly true for transplant programs in Asia, where liver transplantation for HCC is largely reserved as a last resort when other forms of curative treatment are not feasible or have failed. In Asia, where most transplants are from living donors, it may arguably be unethical to risk a healthy donor when there is an alternative option of resection with comparable long-term survival.

**LDLT**

Recent advances in adult LDLT using a right lobe graft have overcome the barrier of size matching between a donor and recipient, and may produce a drastic change in the role of transplantation surgery for HCC. Living donors can potentially provide an essentially unlimited source of liver grafts for a planned transplant operation as soon as the diagnosis of HCC is made. The uncertainty of a long waiting period can be much lessened and the possibility of tumor progression eliminated [44]. Because a live donor graft is a dedicated gift that is directed exclusively to a particular recipient, there is no need for an objective allocation system based on a prioritization scheme.

Before any clinical data were available, hypothetical studies using decision analysis models were conducted to demonstrate the theoretical survival benefit conferred by LDLT over deceased donor liver transplantation (DDLT) for early unresectable HCC [45, 46]. These hypothetical studies, however, neglected the risk to the living donor in the analysis. A systematic review of published data showed that the reported morbidity after donor hepatectomy varied widely from 0%–100%, with a median of 16% [47]. In Asia, donor morbidity was 15% from an international survey [48] and 12% from a multicenter study in Japan [49]. There are, notably, a higher complication rate and a slower recovery with right lobe donation when compared with left lobe donation [49–51]. Furthermore, with such major surgery, mortality is always possible. A search in the medical and lay literature up to February 2006 identified 19 donor deaths; among these, there were 13 cases, together with an additional donor in chronic vegetative state, that were definitely related to donor surgery [52]. The authors estimated that the risk for donor death definitely related to donor surgery is about 0.15% [52].

The role of LDLT and its intention-to-treat survival benefit over DDLT in patients with early HCC have been confirmed in clinical series [53], but several observations have emerged that warrant caution in assuming that the advantage of LDLT is as predicted by hypothetical studies. First, the process of waiting for a living donor is comparable with that of waiting for a deceased donor graft. While the availability of a deceased donor graft depends on a system of organ allocation, the availability of a living donor depends on the family members’ voluntarism and the donor selection criteria. A clinical series from Hong Kong showed that >50% of patients with early HCC might not have a suitable voluntary donor [53]. Second, several recent studies have reported a tendency toward a higher rate of recurrence and lower rate of survival after LDLT for HCC. Roayaie et al. [54] showed that there was a tendency for early tumor recurrence after LDLT (mean time to recurrence, 8.7 months) compared with DDLT (mean time to recurrence, 19.6 months), although the difference was not statistically significant. The multicenter Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) reported a significantly higher recurrence rate within 3 years after LDLT (29%) compared with DDLT (0%) [55]. A report from Hong Kong demonstrated that, despite standard radiological selection criteria based on tumor number and size, patients who underwent LDLT for early HCC had a higher rate of recurrence [43]. Possible explanations for the difference include selection bias for clinical characteristics asso-
associated with aggressive tumor behavior, elimination of natural selection during the waiting period, and enhancement of tumor growth and invasiveness by small-for-size graft injury and regeneration [56, 57]. More clinical studies with long-term follow-up are needed to evaluate the role of LDLT for early HCC.

As a graft from a living donor is a dedicated gift and is not subject to a system of equitable allocation, extending the criteria to include patients with more advanced HCC has been advocated. In fact, most early reports on LDLT for HCC have focused on extended indications [58–61], but as a result of the relatively short follow-up, operative complications and sepsis rather than tumor recurrence were the most common causes of death. The Kyoto group adopted extended criteria that included any size or number of tumors provided there was no gross vascular involvement or distant metastasis detectable at the time of initial evaluation [61]. Their preliminary analysis in 56 patients after a median follow-up of 11 months showed a 1-year survival rate of 73%, and recurrent cancer accounted for only 2 of 16 deaths [61]. Gondolesi et al. [62], from New York, reported that three of 13 deaths in a series of 36 patients were cancer related, and the 1-year survival rate was 75%. More recent multicenter studies from Japan and Korea with larger numbers of patients and longer follow-up provided more useful insight into the outcome of patients with extended indications. In a study by Todo and Furukawa [63] on 316 LDLTs for HCC from 49 centers in Japan, the Milan criteria were adopted by one third of the transplant programs. The 3-year survival rate in patients beyond the Milan criteria was 60.4%, compared with 78.7% in those within the criteria. A similar 3-year survival rate of 62.6% in 62 patients after LDLT for HCC beyond the Milan criteria was reported by Hwang et al. [64] from four liver transplant programs in Korea. In a recent update of the Kyoto series, Takada et al. [65] reported that the 4-year patient survival rate was 64% overall and 59% in 44 of those who were beyond the Milan criteria. While the survival rate is about 15%–20% worse than that of patients meeting the Milan criteria, LDLT does provide a chance of long-term survival for some patients with HCC beyond the Milan criteria when no other treatment options are feasible.

**Liver Transplantation in Asia**

**History**

Liver transplantation in Asia started early and yet progressed slowly when compared with Western countries. The first liver transplant in Asia was performed in 1964 by Nakayama with a graft from a non–heart beating donor in Chiba of Japan [66]. This was only 1 year after Starzl’s historical first attempt in the world at human liver transplantation in Denver, Colorado [67]. It was a highly controversial feat because organ donation from the deceased was not accepted in Japanese culture then. It was not until 1978 that the second transplant in Asia was performed by Lin, Qiu, and Xia in Shanghai, China. From then until the early 1980s, 57 cases in total were subsequently performed in China, mostly for patients with advanced HCC, but there were no long-term survivors [68]. In 1984, Chen, in Taiwan, performed the first liver transplant with long-term survival in Asia at a time when there was still no brain death law in that locality [69]. Legislation regarding brain death was passed in Singapore [70] and Taiwan in 1987 and subsequently in Japan and Korea, thus facilitating the practice of organ transplantation [71].

The development of liver transplantation in Asia was slow. The technology came from the West and it took time for local surgeons returning from training abroad to introduce the procedure in Asia. Transplantation is a demanding discipline requiring extensive manpower, material, and technological resources. In Asia, where most of the countries were classified as developing, transplantation took off earlier in the more affluent ones such as Japan, Hong Kong, Korea, and Taiwan. The biggest barrier, however, was the severe graft shortage because organ donation from the deceased was uncommon. This is mainly a result of various social, cultural, and religious reasons that do not allow the acceptance of brain death nor favor dismembering the body even after death. Funding, civic interest, and government support for organ donation are still lacking in many developing countries. Measures to improve organ donation from the deceased have been implemented, such as training of transplant coordinators, establishment of national organ transplant networks, information and education campaigns involving the media, and encouragement of declaration of intent to donate organs upon death through organ donor cards, driver’s licenses, and insurance documents. However, despite these efforts, organ donation rates in Asian countries have remained among the lowest in the world (Fig. 1), with no significant increase in numbers since 5 years ago [71].

**Asian Contribution to the Development of LDLT**

The critical shortage of deceased donor liver grafts in Asia provides a powerful driving force for the development of LDLT as an alternative option in Asia. The first LDLT in Asia was performed by Nagasue of Shimane University, Japan in 1989 [73], also a year after the first attempt by Raia in Brazil in 1988 [74]. Subsequently Hong Kong, Korea, and Taiwan rapidly initiated pediatric LDLT programs transplanting a left lateral section graft from a parent donor
to a child. The ultimate need for the procedure, however, was in adult recipients. Transplant centers in Asia have repeatedly advanced the frontier of adult-to-adult LDLT. Individual cases of successful adult LDLT using a left lobe graft were first reported from Japan in 1994 [75] and Hong Kong in 1995 [76]. However, the left lobe graft, which comprises only about one third of the entire liver volume, is usually too small for an adult recipient, and it was the availability of the right lobe graft that overcame the barrier of graft size matching for adult recipients. The Kyoto group first reported the use of a right lobe graft for a pediatric recipient as a result of a variance in the donor’s arterial anatomy in 1994 [77]. The first case report [78] and subsequently the first series [79] of successful adult LDLT using a right lobe graft were reported from Hong Kong in 1997. Further technical advances in adult LDLT, including the addition of the caudate lobe to a left lobe graft [80] and the use of right lateral sector grafts [81], were reported from Japan. An attempt to provide adequate graft function for an adult recipient and minimize the risk of an individual donor, dual grafts from two donors for one recipient was introduced in Korea [82]. The minimum sizes of the graft in the recipient [83, 84] and the remnant in the donor [85] were also described in Asian studies.

Overview of Experience with Liver Transplantation

There is no international registry for liver transplantation in Asia. Some countries, such as Japan, Korea, and Taiwan, have national registries for organ transplantation in general. Only China and Japan have national registries specifically for liver transplantation [86, 87]. The majority have their own individual institution databases and there is no managed centralized source of regional information on liver transplantation. An international survey on liver transplantation in Asia (Hong Kong, India, Japan, Korea, mainland China, Malaysia, The Philippines, Singapore, Saudi Arabia, and Taiwan) was conducted in 2006, and the results were presented at the 12th Annual Congress of the International Liver Transplantation Society in Milan (Chung Mau Lo, unpublished data). The situation is unique in mainland China, where a large number of liver transplants were performed using deceased donor grafts and the practice of LDLT has just been initiated [68]. Hence, if the data from mainland China are excluded, the number of liver transplantations from deceased donors in Asia has remained almost static (80–140 cases each year) over the past decade (Fig. 2). On the other hand, there has been a sharp rise in the annual number of LDLTs since late 1990s when right lobe LDLT for adult recipients was introduced, and the annual number has increased by more than 10-fold to 1,387 cases in the year 2005. By the end of 2005, 7,237 cases of LDLT had been performed, and LDLT comprised >90% of liver transplants (1,387 of 1,526 in the year 2005) in Asia. For comparison, LDLT accounted for <5% of all liver transplant operations in the U.S. [88].

Liver Transplantation for HCC in Asia

To assess the experience with liver transplantation for HCC in Asia, a separate survey involving major liver transplant centers in the region was conducted in January 2007. The respondents included the Asan Medical Center in Seoul, Asian Centre for Liver Disease and Transplantation in Singapore, Catholic University of Korea in Seoul, Chang Gung Memorial Hospital in Kaohsiung, University of Hong Kong Medical Centre in Hong Kong, and Seoul National Univer-
sity in Seoul. Data from Japan and mainland China were obtained from the Japanese Survey of LDLT for HCC based at the Hokkaido University and the China Liver Transplant Registry [86], respectively.

The pooled data showed that, by the end of 2005, 1,259 (28%) of 4,462 liver transplants in adults over a 12-year period were performed for patients with HCC (Fig. 3). The proportion has been rising, from about 12% before 2001 to about 33% in the last 4 years. In mainland China, in particular, about half of the liver transplants were performed in patients with HCC [86]. These figures from Asia contrast sharply with those from the West. HCC was the indication for transplantation in only about 9% of patients in the pre-MELD and 22% in the early post-MELD period in the U.S. [89]. An update from the OPTN database showed that from January 2003 to December 2006 the rate of liver transplantation for HCC in the U.S. was 21.5% (Erick Edwards, United Network for Organ Sharing, personal communication). However, the poor accuracy of diagnosis of HCC based on pretransplant imaging studies has been recognized, and as many as 21% of cases without any pretransplant ablative treatment were found to have no HCC on histopathologic examination [21]. In Europe, only about 10% of patients undergo liver transplantation for HCC [90].

As is true for liver transplant in general, a large number of DDLTs were performed for HCC in mainland China [86]. When the data in mainland China are excluded, almost all liver transplants for HCC in Asia were performed using live donor grafts (Fig. 4). In fact, in the year 2005, 96% (331 of 344) of transplants for HCC were from live donors. As discussed previously, unlike in the U.S., where recipients with malignancies receive extra prioritization in the deceased donor organ allocation scheme [91], HCC patients in Asia do not. HCC patients in Asia have a dismal chance of receiving a deceased donor graft and LDLT is often the only option.
Many transplant centers in Asia accept patients with extended criteria. Even in centers that have adopted the Milan or UCSF criteria [43, 92–94], patients with extended criteria are considered on a case-by-case basis, taking into account the presence of risk factors for recurrence individually and the wishes of the patient and his/her family, especially when they strongly request LDLT. The centers surveyed have evaluated their outcomes according to the Milan criteria. Table 1 shows the 3-year survival rates of patients within and beyond the Milan criteria. The outcomes in patients within the criteria were all >75%. Patients beyond the Milan criteria had a survival rate in the range of 22%–100%, with an average of about 60%.

CONCLUSION
The high incidence of HCC and the low organ donation rate in Asia have created a distinctive pattern of indication and strategy in the application of liver transplantation. HCC will continue to grow as an indication for liver transplantation. Promotion of organ donation is necessary, but LDLT as the dominant strategy will keep on escalating. Without the need for prioritization of organ allocation, more transplant centers are likely to extend the selection criteria to include patients with advanced tumors. While arguing for and respecting the autonomy of the decision of the donor and recipient, the benefit of LDLT for extended indications is poorly quantified. Hence, there is a need to undertake vigilant data collection and evaluation in order to have more clinical studies on the long-term outcome and predictors of recurrence. The practice of liver transplantation for HCC in Asia will continue to evolve.

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**Table 1.** Three-year survival rates of hepatocellular carcinoma patients within and beyond the Milan criteria who underwent liver transplantation in Asia

<table>
<thead>
<tr>
<th>Country</th>
<th>Institution</th>
<th>Overall</th>
<th>Within Milan criteria</th>
<th>Beyond Milan criteria</th>
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<tr>
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<td>n (%)</td>
<td>n (%)</td>
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<td>Japan</td>
<td>Multicenter</td>
<td>653a</td>
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<td>394 (80)</td>
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<td>76</td>
<td>196 (79)</td>
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<td>104a</td>
<td>68</td>
<td>75 (76)</td>
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<td>84</td>
<td>56 (88)</td>
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<td>Chang Gung Memorial Hospital Kaohsiung</td>
<td>35</td>
<td>96</td>
<td>34 (95)</td>
</tr>
<tr>
<td>Singapore</td>
<td>Asian Centre for Liver Disease and Transplantation</td>
<td>21</td>
<td>33</td>
<td>6 (83)</td>
</tr>
</tbody>
</table>

aSome patients have missing data for tumor classification according to the Milan criteria.
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