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Review

Living Donor Liver Transplantation for Patients with Hepatocellular Carcinoma

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Key Words
Deceased donor liver transplantation · Hepatocellular carcinoma · Living donor liver transplantation · Living donors · Recurrence

Abstract
Background: Liver transplantation has become an established treatment for cirrhotic patients with hepatocellular carcinoma (HCC), and the Milan criteria are now widely accepted and applied as an indication for deceased donor liver transplantation (DDLT) in Western countries. In contrast, however, due to the severe organ shortage, living donor liver transplantation (LDLT) is mainstream in Japan and in other Asian countries. ***Summary:*** Unlike DDLT, LDLT is not limited by the restrictions imposed by the nationwide allocation system, and the indication for LDLT in patients with HCC often depends on institutional or case-by-case considerations, balancing the burden on the donor, the operative risk, and the overall survival benefit for the recipient. Accumulating data from a nationwide survey as well as individual center experience indicate that extending the Milan criteria is warranted. ***Key Messages:*** While the promotion of DDLT should be intensified in Japan and other Asian countries, LDLT will continue to be a mainstay for the treatment of HCC in cirrhotic patients.

Introduction

Hepatocellular carcinoma (HCC) is the seventh most common cancer overall and the third most common cause of cancer-related death worldwide [1, 2]. HCC usually coexists with liver cirrhosis, which is most commonly secondary to hepatitis C virus (HCV) or hepatitis B virus (HBV) infection or other diseases, such as alcoholic liver disease and autoim-

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mune disease. Liver transplantation (LT) is now widely accepted as an effective treatment modality for HCC, especially in patients with cirrhosis, which often precludes conventional locoregional treatment [3–7].

Early reports of LT as a treatment for HCC were associated with poor outcomes [8, 9], reflecting the advanced HCC status of the recipients indicated for LT. The landmark study by Mazzaferro et al. [10], however, demonstrated that survival rates after LT among selected HCC patients were equivalent to those of patients transplanted for non-malignant liver disease. In that study, 48 LT recipients having a single tumor smaller than 5 cm in diameter or up to three tumors smaller than 3 cm in diameter with no vascular invasion or extra-hepatic disease, as determined by preoperative imaging studies, had actuarial 4-year disease-free and overall survival rates of 83% and 75%, respectively. These criteria, called the Milan criteria, are the gold standard indication for LT in patients with HCC. Recently, Mazzaferro and associates [11] reported that the Milan criteria comprise an independent prognostic factor for long-term outcome after LT for HCC based on a systematic review of the literature encompassing 15 years of experience and including 3949 LT recipients. At a recent international conference of expert panels, the Milan criteria were concluded to be the gold standard indication for LT in recipients with HCC and the basis for comparison with other investigated criteria [12].

On the other hand, however, there has been ongoing debate as to whether the Milan criteria are too strict, thereby precluding patients with HCC from LT who could otherwise benefit from LT, and many investigators have performed studies extending the Milan criteria with satisfactory results. The issue of extending the criteria for patients with HCC is a crucial topic for cadaveric LT in Western countries [13].

In Asian countries, living donor liver transplantation (LDLT) makes up the majority of LT cases, and thus the situation differs from that of Western countries [14–16]. Grafts from living donors are not limited by restrictions imposed by the organ allocation system, meaning that the relation of the graft and recipient is usually one-on-one. Consequently, selection criteria based on the tumor burden, such as the tumor size and tumor number, can be considered relative on a case-by-case basis, taking into account the presence of risk factors for recurrence and the chance of survival, as well as the wishes of the donor. In fact, many high-volume LT centers in Asia already perform LDLT for patients with HCC based on extended Milan criteria [7]. The present review covers recent topics regarding LT for HCC with special reference to LDLT for HCC in Japan and other Asian countries.

Factors Associated with HCC Recurrence after LT

Despite every effort to minimize recurrence by the careful selection of HCC patients for LT, HCC recurrence after LT remains a clinically important problem. Based on the literature, HCC recurrence after LT uniformly occurs with an incidence of 10–20% [17]. In one study of 60 LT recipients, median overall survival after recurrence was 10.5 months (range 1–136 months), and only late recurrence and eligibility for surgical resection were positively correlated with survival [18].

Well-recognized predictors of recurrence include tumor size and number, bilobar disease, tumor differentiation, presence of macro- and microvascular invasion and tumor satellites, and tumor-specific biomarkers such as alpha-fetoprotein (AFP) levels before LT [10, 19–29]. Gross features of HCC, including the tumor size and number, which are part of the Milan criteria, are critical. A recent meta-analysis of 74 studies involving 22,432 patients revealed that assessment of the diameter of the largest nodule or the total diameter of nodules

was the best predictor of outcome, and that a total tumor size (sum of diameters) greater than 10 cm was associated with a fourfold higher risk of recurrence [30]. Another meta-analysis of 1198 patients indicated that the presence of vascular invasion, poor differentiation, tumor diameter greater than 5 cm, and tumor status beyond the Milan criteria were independent risk factors for HCC recurrence [31]. Although tumor differentiation and the presence of microvascular invasion are recognized as important risk factors for HCC recurrence after LT, these features are usually not able to be determined until after explantation of the liver. Saborido and colleagues [32] reported a higher recurrence rate among patients who underwent tumor biopsy before LT. Currently, pre-transplant tumor biopsy is not required in cirrhotic patients considered for LT who have high-quality dynamic computed tomography (CT) or magnetic resonance image (MRI) findings typical for HCC [12]. Biomarkers such as AFP and des-gamma carboxy prothrombin (DCP) are reported to correlate with post-LT recurrence of HCC [21, 28, 33, 34]. A recent study using the Organ Procurement and Transplant Network database recommends adding AFP level greater than 400 ng/ml to total tumor volume as a predictor of outcome after LT for HCC [28]. A French group also proposed that the prediction of HCC recurrence after LT is significantly improved by applying modified Milan criteria that incorporate the AFP level [21]. Recently, micro-RNA clusters were extensively investigated as a biomarker representing the biologic behavior of HCC [35, 36] in association with recurrence.

Another important issue regarding risk factors for HCC recurrence following LDLT is that LDLT itself could be a risk factor for recurrence compared with deceased donor liver transplantation (DDLT). A large multicenter cohort study from Japan [37] and Korea [38] demonstrated that application of the Milan and University of California, San Francisco, (UCSF) criteria to LDLT yielded an equivalent long-term outcome to that for DDLT, but some authors [39, 40] recently reported a higher incidence of HCC recurrence in LDLT recipients compared with DDLT recipients.

Eligibility of Extended Criteria for DDLT

Reports of proposed extended Milan criteria, which are in some cases already commonly used, are summarized in table 1 [19, 27, 28, 41–44]. Among these, the UCSF criteria, initially reported by Yao et al. in 2001 [27], are well-recognized extended Milan criteria that have been applied to clinical practice; the UCSF criteria are patients with a solitary tumor ≤ 65 mm in diameter, or two or three tumors, each with a diameter ≤ 45 mm and a total tumor diameter ≤ 80 mm. According to Yao et al., patients meeting the UCSF criteria had an overall survival rate of 90% and 73% at 1 and 5 years after LT, respectively [27]. Although the initial UCSF criteria were reported based on pathologic examination of the explant, the same authors validated their eligibility based on pre-LT imaging studies. Subsequent studies validated the UCSF criteria in a larger cohort.

Recently, Mazzaferro and colleagues [44] introduced the “Up-to-seven” criteria, based on a multicenter study of 1556 LT recipients: patients with the total number of tumor nodules added to the diameter of the largest nodule (in cm) not exceeding 7 had a 5-year survival rate of 70%, equivalent to that of the Milan criteria.

DuBay and associates [19] reported the Toronto criteria, which incorporate tumor biopsy: patients with HCC beyond the Milan criteria are still eligible for LT provided that those with a poorly differentiated tumor are excluded. Using this approach, the 5-year overall survival and disease-free survival rates were 72% and 70%, respectively, in those within the Milan criteria, and 70% and 66%, respectively, in those not limited by tumor number or size [19].

Table 1. Reports comparing outcomes between extended criteria and Milan criteria in the DDLT setting

Reference (year)	Eligibility criteria	Tumor characteristics and the number of cases included	Overall survival (%)		
			1 year	3 years	5 years
Yao et al. (2001) [26]	Solitary tumor with diameter ≤6.5 cm	Within extended criteria n=60	90		75
UCSF criteria	Tumors up to three nodules with maximum diameter ≤4.5 cm, and total tumor diameter ≤8 cm	Within Milan n=51	91		72
Mazzaferro (2009) [43]	Sum of the number of nodules and diameter of the largest nodule (in cm) ≤7	Within extended criteria, beyond Milan, and without microvascular invasion n=283		66	71
Up-to-seven criteria		Within extended criteria, beyond Milan, and with microvascular invasion n=116		60	47
		Within Milan and without microvascular invasion n=362		82	76
		Within Milan and with microvascular invasion n=44		77	72
DuBay (2011) [18]	Unrestricted tumor size or number	Within extended criteria and beyond Milan n=105			70
Toronto criteria	Not poorly differentiated histology on biopsy (tumors beyond Milan only)	Within Milan n=189			72
Herrero et al. (2008) [40]	Solitary tumor with diameter ≤6 cm	Within extended criteria and beyond Milan n=26	88	72	68
	Tumors up to 3 nodules with maximum diameter ≤5 cm	Within Milan n=59	88	73	66
Toso et al. (2008) [27]	Total tumor volume ≤115 cm^3	Within extended criteria n=251			80
		Within Milan n=157			82
Silva et al. (2008) [41]	Tumors up to 3 nodules with maximum diameter ≤5 cm, and total tumor diameter ≤10 cm	Within extended criteria and beyond Milan n=26	92	79	69
		Within Milan n=231	82	68	69
Zheng et al. (2008) [42]	Total tumor diameter ≤8 cm	Within extended criteria n=99	93	71	71
	Total tumor diameter ≤8 cm, with grade I or II tumor on biopsy and AFP ≤400 ng/ml	Within Milan n=72	94	78	78

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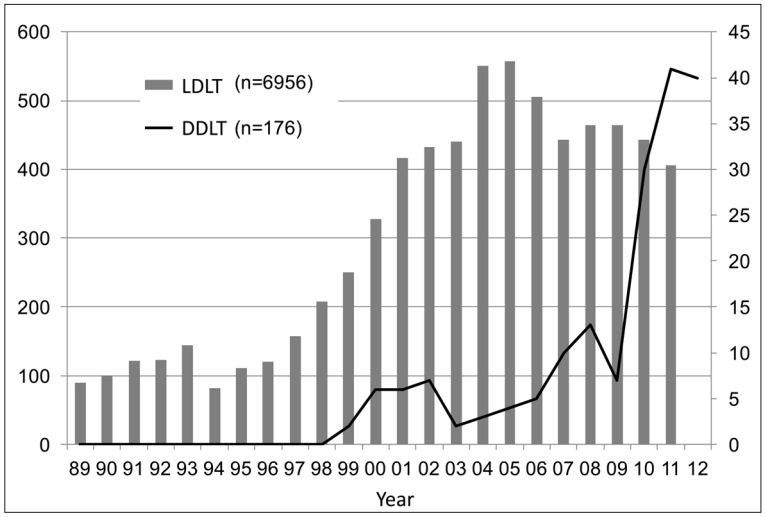

Fig. 1. Changes in the number of liver transplant cases in Japan.

To date, although many expanded criteria have been proposed, as shown in table 1, only the Milan criteria have been widely validated and accepted as a gold standard worldwide. The main problem associated with expansion or modification of the Milan criteria is that tumor characteristics, such as microvascular invasion and tumor differentiation, cannot currently be evaluated reliably prior to LT [12]. Any expansion must be balanced with its effect, in terms of organ allocation, on the survival of candidates for LT who do not have HCC [16, 45].

LDLT for HCC in Japan

The Japanese Ministry of Health, Labour, and Welfare considers LT indicated for patients with HCC within the Milan criteria, stating that (1) the decision of whether the patient satisfies the Milan criteria should be based on dynamic CT or MRI taken within 1 month before LT, (2) a pre-LT diagnosis of HCC means that the tumor demonstrates the classical pattern, low-high-low density on dynamic contrast-enhanced CT, (3) and in patients who undergo locoregional treatment prior to LT, at least a 3-month interval between the last treatment and LT is mandatory (tumors judged as totally necrotic need not be counted). All Japanese institutions, however, allow patients whose tumor status is beyond the Milan criteria to undergo LT according to the institution's criteria, as described previously, as an uninsured treatment, provided that there is no contraindication such as macroscopic vascular invasion or extrahepatic metastases [46].

In Japan, even though the brain-death law was passed in 1997, there remains a crucial shortage of deceased donors. Only 176 DDLTs had been performed by the end of 2012, whereas 6956 LDLTs were performed within the same period (fig. 1). LDLT is widely accepted and applied for the treatment of HCC, and it is also incorporated within the Japanese guidelines [47] for HCC management, just as DDLT is in Western countries [4]. According to a report from the Japanese Liver Transplantation Society Registry [48], a total of 6097 LDLTs had been performed in Japan by the end of 2010. Of these, 3873 (64%) were performed in adult patients (over 18 years old), and 1225 (32%) were indicated for HCC, which was the most common indication in adult patients. The 1-, 3-, 5-, and 10-year cumulative survival rates of LDLT for HCC are 85%, 74%, 69%, and 60%, respectively. When stratified by the Milan criteria, there is

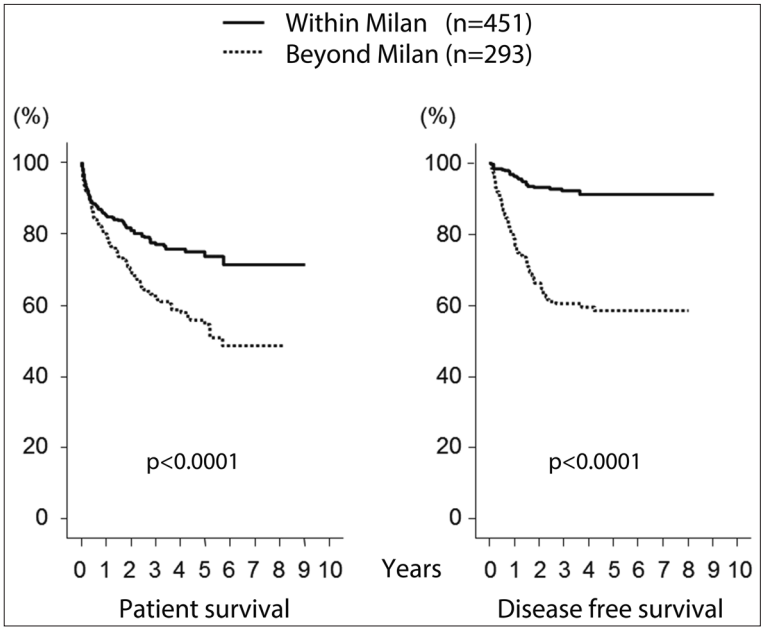

Fig. 2. Patient survival and recurrence-free survival stratified by the Milan criteria.

a significant difference between those within the Milan criteria and those beyond the Milan criteria (fig. 2). These findings are comparable with those found in the DDLT databases of the United States [49] and Europe [50]. Todo and colleagues [51] performed a detailed survey using the same database (up to the end of 2005) of 653 patients who had undergone LDLT for HCC in Japan. HCV infection was the leading cause of HCC, accounting for 385 (59%) recipients. At 1, 3, and 5 years, overall patient survival was 83%, 73%, and 69%, and disease-free survival was 77%, 65%, and 61%, respectively. Based on preoperative imaging studies, 62% of these 653 patients were within the Milan criteria and 38% were beyond the Milan criteria, with 5-year recurrence-free survival rates of 90% and 61%, respectively ($p<0.001$). The tumor recurred in 92 (14%) LT recipients, with a cumulative recurrence rate at 1, 3, and 5 years of 9%, 20%, and 22%, respectively. In a multivariate analysis, preoperative AFP and DCP levels were determined to be independent risk factors for HCC recurrence.

Despite insurance coverage for LT for HCC being limited to patients who fulfill the Milan criteria in Japan, each center has developed and proposed expanded selection criteria based on institutional and regional experience, as mentioned above. The proposed extended criteria from three major transplant centers in Japan are summarized in table 2 [52–54].

At our institution, the University of Tokyo Hospital, a total of 423 adult recipients had undergone LDLT by the end of 2012. Among them, 125 (30%) patients had HCC. The principle criterion for LDLT for HCC at our center is "up to five nodules with a maximum tumor diameter of 5 cm," which we call the five–five rule [52]. Of the 125 HCC patients, 118 (94%) were within the five–five rule criteria and 109 (87%) were within the Milan criteria. Overall survival of the 125 recipients at 1, 3, and 5 years was 88%, 82%, and 76%, respectively, with a median follow-up period of 8 years. There was no difference in the overall survival rate between patients with HCC and those without HCC at our institution (fig. 3). A total of 11 (9%) patients developed HCC recurrence with a cumulative recurrence rate at 1, 3, and 5 years of 6%, 9%, and 11%, respectively. In the multivariate analysis for HCC recurrence, tumors not within the five–five rule, AFP level >400 ng/ml, and DCP level >200 mAU/ml were independent risk factors within our cohort.

Table 2. Reports of LDLT for HCC from high-volume Asian centers

Reference (year)	Eligibility criteria	Tumor characteristics and number of cases included	Overall survival (%)		
			1 year	3 years	5 years
Reports from Japan					
Present report	Tumors up to 5 nodules with maximum diameter ≤5 cm	Within extended criteria n=118	89	81	80
Tokyo		Within Milan n=109	88	79	78
Kaido et al. (2013) [52]	Tumor with diameter ≤5 cm, up to 10 nodules, and DCP ≤400 mAU/ml	Within extended criteria n=147			82
Kyoto		Within Milan n=118			76
Shirabe et al. (2011) [53]	Tumor with diameter ≤5 cm or DCP ≤300 mAU/ml	Within extended criteria n=89	92	86	83
Kyushu	Unrestricted tumor number	Within Milan n=36	100	83	83
Reports from other Asian countries					
Lee et al. (2008) [57]	Tumors up to 6 nodules with maximum diameter ≤5 cm	Within extended criteria n=186			76
Korea		Within Milan n=164			76
Concejero et al. (2008) [55]	Milan criteria	Within Milan n=35	98	96	90
Taiwan					
Ng et al. (2010) [56]	UCSF criteria	Within UCSF and beyond Milan n=33	100	73	65
Hong Kong		Within Milan n=50	96	83	72

The Kyoto group [53] proposed extending the selection criteria to "Within 10 nodules, all tumor diameters within 5 cm, and DPC levels under 400 mAU/ml." A total of 198 HCC patients underwent LDLT, and among those, 147 (82%) were within the Kyoto criteria, whereas 118 (76%) met the Milan criteria. The 5-year survival rate of those within the Kyoto criteria was 82%, while that of those beyond the Kyoto criteria was 42% ($p<0.001$). In contrast, the 5-year survival rate for those within the Milan criteria was 76%, which was not statistically different from the 65% figure for those beyond the Milan criteria ($p=0.3$).

The Kyushu group [54] proposed extending the criteria to "A maximum diameter of the tumor of less than 5 cm without limiting the number of nodules, and DCP levels under 300 mAU/ml." A total of 109 HCC patients underwent LDLT, and among those, 103 patients (94%) were within the Kyushu criteria, whereas 55 (50%) met the Milan criteria. The 5-year recurrence-free survival of patients who met the Kyushu criteria was 71%, whereas all six patients beyond the Kyushu criteria developed recurrent HCC within 2 years. The 5-year recurrence-

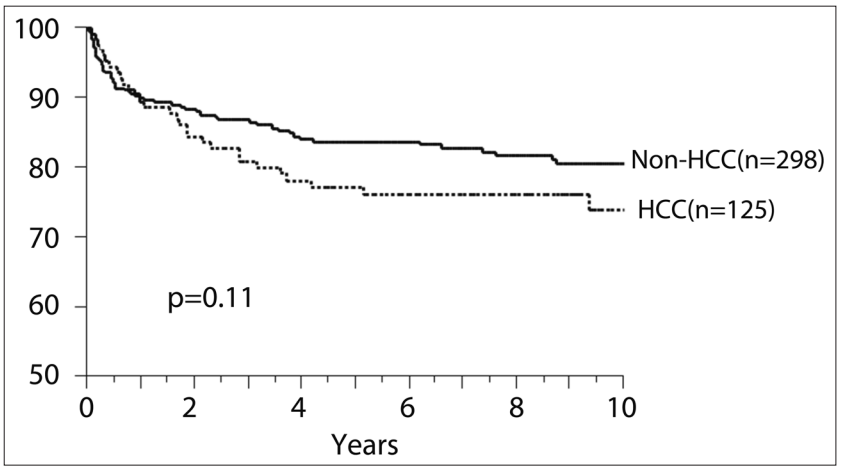

Fig. 3. Patient survival after LDLT at the University of Tokyo Hospital.

free survival of those within the Kyushu, but beyond the Milan criteria (n=48), was 80%, while that of those beyond both the Kyushu and Milan criteria (n=6) was 0%.

LDLT for HCC in Asian Counties

In other Asian countries, as in Japan, the majority of LT for HCC patients are LDLT, and these account for 96% of LT for HCC [14]. Apart from the predominance of hepatitis B-related HCC [7, 55], the situation in other Asian countries is similar to that in Japan. The Taiwan group adopted the Milan criteria as an indication for LDLT [56], while the Hong Kong group adopted the UCSF criteria [57]. The Asan group of Korea, just like Japanese institutions, advocates its own criteria, specifically, "the tumor number should be up to six nodules and the maximum diameter of the tumor is limited to within 5 cm" [58]. The reports from these centers are summarized in table 2.

Notably, all Asian expanded criteria restrict the maximum diameter of the tumor to 5 cm for the indication for LDLT, whereas there is a large discrepancy regarding the maximum number of tumors. Two large historical retrospective studies [59, 60] revealed that tumors greater than 5 cm in diameter result in a high recurrence rate after LT, mainly due to the association between tumor size and vascular invasion/poor differentiation. Recently, the association between vascular invasion and the size of the nodule was confirmed: a study found that microscopic vascular invasion was present in 20% of tumors smaller than 2 cm in diameter, in 30–60% of tumors of 2–5 cm, and in up to 60–90% of nodules greater than 5 cm in diameter [61]. These findings support the basis for keeping the maximum tumor size at 5 cm while expanding the limit for the maximum number of tumors in Asian countries.

Conclusions

The high prevalence of viral infection and subsequent high incidence of HCC combined with the low organ donation rate from deceased donors in Japan and in other Asian countries have led to the need for unique indications and strategies for application of LT in the region. While the promotion of DDLT should be intensified in Japan and other Asian countries,

LDLT will continue to be a mainstay treatment of HCC in cirrhotic patients. Expansion of the criteria for the indication of LT for HCC patients is a matter of debate regarding LDLT in Asian countries and DDLT in Western countries.

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