

# Living donor liver transplantation for patients with hepatocellular carcinoma—20 years after introduction of the Milan criteria

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## Introduction

The reported outcome of liver transplantation for hepatocellular carcinoma (HCC) is poor (1,2), mainly because there is no limitation of the HCC status in patient selection. Mazzaferro *et al.* (3), however, demonstrated that survival rates after liver transplantation among HCC patients were equivalent to those for non-HCC patients when properly selected according to tumor status (single tumor <5 cm in diameter or up to 3 tumors <3 cm in diameter with no vascular invasion or extra-hepatic disease determined on imaging). The 4-year disease-free and overall survival rates were 83% and 75%, respectively. These criteria, the so-called the Milan criteria, have been the gold standard indication for transplantation in patients with HCC. In 2011, Mazzaferro *et al.* (4) reviewed the literature and reported that the Milan criteria were independent prognostic factors for the long-term outcome after transplantation for patients with HCC. A recent international conference of expert panels concluded that the Milan criteria continue to be the gold standard indication for transplantation in recipients with HCC (5).

Twenty years have now passed since the introduction of the Milan criteria (3), but there is ongoing debate about whether the Milan criteria are too strict. The Milan criteria exclude patients who could potentially benefit from transplantation. Some studies have proposed extending the Milan criteria with satisfactory results.

In Asian countries, liver transplantation using grafts from living donors (LDLT) comprises the majority of transplantations and thus the situation differs from that in Western countries (6,7). LDLT is a private issue among the

patients and their families. The grafts are not restricted or imposed by the public organ allocation system, and thus selection criteria based on the tumor status, such as the tumor size and tumor number, may be considered relative on a case-by-case basis. The presence of risk factors for recurrence and the chance of survival, as well as the donor's will to donate the liver should be taken into account. In fact, many high-volume liver transplantation centers in Asia already perform LDLT for patients with HCC based on extended Milan criteria (8).

## Liver transplantation for HCC in Japan

The Japanese Ministry of Health, Labor, and Welfare set the HCC tumor status covered by the insuring system in patients who undergo transplantation based on the Milan criteria. The guideline states that (I) tumor status should be diagnosed by dynamic computed tomography or magnetic resonance imaging obtained within 1 month before transplantation; (II) qualitative diagnosis should be based on the so-called classical pattern, i.e., low density in plain, high in arterial phase, and low in portal phase in dynamic computed tomography; and (III) when local treatment for HCC is performed before liver transplantation, there must be at least a 3-month interval between the last treatment and transplantation. Many Japanese institutions, however, have their own criteria and allow patients with a tumor status beyond the Milan criteria to undergo transplantation when there is no contraindication, such as macroscopic vascular invasion or extrahepatic metastases (9).

In Japan, the serious shortage of deceased donor

livers continues despite approval of the Japanese Organ Transplantation Act in 1997. According to a report from the Japanese Liver Transplantation Society Registry (10), by the end of 2015, only 321 liver transplantations were performed using deceased donor grafts, while 8,066 LDLTs were performed during the same period. LDLT is widely accepted and applied for the treatment of HCC in Japan. Of these transplantations, 1,551 were indicated for HCC, and the 1-, 3-, 5-, 10-, 15- and 20-year survival rates of LDLT for HCC are 85%, 75%, 70%, and 62%, 54%, and 54%, respectively.

In 2007, Todo *et al.* (11) performed a survey using a database comprising the 653 patients who underwent LDLT for HCC in Japan between 1990 and 2005. At 1 year, 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, 62% were within the Milan criteria and 38% were beyond the criteria. The 5-year recurrence-free survival was 90% and 61% for those fulfilling and not fulfilling the Milan criteria, respectively, with a significant difference between them ( $P < 0.001$ ). HCC tumors recurred in 92 (14%) recipients, with a recurrence rate at 1 year, 3, and 5 years of 9%, 20%, and 22%, respectively. In the multivariate analysis, preoperative alpha-feto-protein and des-gamma-carboxy-prothrombin levels were determined to be independent risk factors for HCC recurrence.

Insurance coverage for liver transplantation for HCC in Japan is limited to patients who fulfill the Milan criteria. Each center, however, has developed and proposed new criteria that expand the Milan criteria based on regional experience.

The principle criterion I have adopted for LDLT for HCC at our center is “5 nodules or fewer than 5 nodules with a maximum diameter of 5 cm” (12), referred to as the ‘5-5 rule’. Of 125 HCC patients, 118 (94%) were within the 5-5 rule criteria and 109 (87%) were within the Milan criteria. Overall survival of the 125 patients was 88%, 82%, and 76% at 1 year, 3, and 5 years, respectively. The median follow-up period was 8 years. There was no difference in the overall survival rate between patients with HCC and those without HCC at our institution. Eleven patients (9%) developed HCC recurrence with a rate of 6%, 9%, and 11% at 1 year, 3, and 5 years, respectively. Multivariate analysis for recurrence revealed that tumors beyond the 5-5 rule, alpha-feto-protein level over 400 ng/mL, and des-gamma-carboxy-prothrombin over 200 mAU/mL were independent risk factors.

## Conclusions

The scarcity of deceased donors in Japan has stimulated the search for unique indications and strategies in liver transplantation. Although a broader application of liver transplantation from deceased donors is necessary, LDLT will continue to be a mainstay treatment for patients with HCC and liver cirrhosis. Expansion of the criteria for the indication of transplantation in patients with HCC remains under debate in Japan.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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