Hepatic Oncology

Liver transplantation for advanced hepatocellular carcinoma: how far can we go?

Kyung-Suk Suh^{*1} & Hae Won Lee^{1,2}

Practice Points

- Living donor liver transplant (LDLT) should be considered in patients with advanced hepatocellular carcinoma (HCC) if there are no other effective treatment options and if patients are expected to benefit from liver transplantation (LT).
- HCC patients with favorable tumor biology should not be excluded from LT, particularly LDLT, solely because they are beyond the Milan criteria.
- According to our experience, LDLT can be performed even in patients with far-advanced HCC including PVTT, resulting in satisfactory outcomes if tumor biology is favorable.
- A combination of surgical resection, mTOR inhibitor and sorafenib could enhance long-term survival in patients even after post-transplant HCC recurrence.
- We are expanding the indication of LDLT to patients with far-advanced HCC in selected situations.
- Currently, the only absolute contraindication for LDLT at our center is extra-hepatic metastasis.

SUMMARY Liver transplantation is one of the most effective treatment options for hepatocellular carcinoma. Although the Milan criteria have been widely used to identify suitable candidates for liver transplant with a good prognosis, many transplant centers have developed and actually used more expanded criteria. Living donor liver transplant (LDLT) is at the center of expansion of criteria because it is based on the personal relationship between a recipient and a donor. Asian LDLT centers have developed various expanded criteria for LDLT using tumor biologic markers as well as the size and number of the tumors. However, there is no consensus on the limit of the expansion of criteria. Here, we present our experience and opinion on LDLT for advanced hepatocellular carcinoma.

Liver transplantation (LT) is one of the accepted treatment modalities for hepatocellular carcinoma (HCC) [1,2]. The advantage of LT is that both the tumor and the underlying disease are treated at the same time, regardless of hepatic insufficiency, resulting in the restoration of liver function and a decrease in the risk of *de novo* HCC [3]. However, the initial results of LT for HCC were disappointing due to high recurrence rates [4–7]. In 1996, Mazzaferro *et al.* [8] suggested that LT should be limited to patients with early HCC characterized by no major vessel invasion and a single tumor less than 5 cm in size, or three or fewer tumors with the largest tumor less than 3 cm in size, referred to as the Milan criteria. They showed that good 4-year overall and recurrence-free survival rates of 75 and 83% respectively, were obtained when LT was performed for early HCC [8]. These Milan criteria are even now widely used to identify suitable candidates for LT with a good prognosis. Nonetheless, many investigators have pointed out that the Milan criteria are too restrictive. Hence, variable expanded criteria for LT for HCC have been suggested [9–14]. However, it is still unclear which criteria are the most effective for selecting good candidates. In addition, there is no consensus on the acceptable patient survival after LT, especially living donor liver transplant

KEYWORDS

- advanced hepatocellular carcinoma
- AFP
- criteria
- indication
- living donor liver transplantation
- positron emission tomography
- PIVKA-II
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¹Department of Surgery, Seoul National University College of Medicine, Seoul, South Korea

²Department of Surgery, Seoul National University Boramae Medical Center, Seoul, South Korea

^{*}Author for correspondence: Tel.: +82 2 2072 3789; Fax: +82 2 766 3975; kssuh@plaza.snu.ac.kr

(LDLT). It has been reported that excellent long-term outcomes could be expected, even in patients with advanced HCC beyond the Milan criteria, if the tumor biology is favorable [15–17]. Therefore, the type of LT and biologic features as well as the size and number of the tumors should be considered before making the final decision regarding LT for HCC.

Expanded criteria for LT for HCC & LDLT

Since the adaptation of the Milan criteria, the outcomes of LT for HCC have improved significantly and are comparable to those for non-malignant indications [18–20]. However, it has been constantly emphasized that these strict selection criteria might exclude a significant number of patients with HCC who could benefit from LT [14,21–25]. The most representative expanded criteria were the University of California San Francisco (UCSF) criteria proposed by Yao *et al.* [14] in 2001, that is, one lesion ≤ 6.5 cm in diameter, or two to three lesions, each ≤ 4.5 cm in diameter, with a total diameter of ≤ 8 cm. They showed that the 5-year overall survival rate of patients with HCC meeting their expanded criteria was 75.2%, which was not inferior to results obtained by the Milan group. Thus they concluded that the Milan criteria may be modestly expanded while still preserving excellent survival after LT [14]. Eventually the Milan group also attempted to expand their original criteria and suggested a new set: known as the up-to-seven criteria [26]: tumors with seven as the sum of the size of the largest tumor (in cm) and the number of tumors. In their study, the up-to-seven group achieved a 5-year overall survival rate of 71.2%, which was comparable to their previous results based on the Milan criteria [26]. The UCSF criteria and the up-to-seven criteria were validated as a useful model for evaluating potential candidates for LT by many worldwide transplant centers after initial suggestions [27–33].

Liver grafts of deceased donors should be allocated to patients in whom an acceptable post-LT survival is expected, because of the ethical aspects. Therefore, LT for HCC could be justified only when the results are comparable to those for non-malignant indications. Hence, expansion of criteria for LT for HCC inevitably has social limitations under the circumstances of deceased donor LT. Not only the Milan criteria but also the UCSF and up-to-seven criteria were designed for deceased donor LT. These criteria cannot be applied to

LDLT [34]. In fact, many Asian LDLT centers have different LDLT criteria for HCC [9–13]. LDLT can only be performed depending on the voluntary desire and strong request of a donor, which is based on the donor–recipient personal relationship. A potential liver graft is dedicated to only one recipient. Therefore, lower post-LT survival can be socially acceptable under the circumstances of LDLT. However, even in LDLT, there can be debates about expanding the criteria for HCC because LDLT is accompanied by donor risk. The estimated rate of donor death was 0.15 to 0.20% [35] and donor complication rates reported to be up to 78% [36,37,38,39,40]. Bruix *et al.* [41] emphasized that in consideration of the donor risk, even LDLT should be performed only when post-transplant survival of more than 50% can be expected. Hence, even in Asian LDLT centers, the criteria were expanded to yield results comparable to those of the Milan criteria [9–13]. Nonetheless, there is still no consensus on whether or not patients with advanced HCC should be rejected for LDLT. In patients with advanced HCC, LDLT might be the only treatment option to expand their life expectancy although the recurrence risk is high. Furthermore, some patients with favorable tumor biology could have long-term recurrence-free survival [15–17], and the recent introduction of mTOR inhibitor and targeted agents could improve survival after recurrence [24,42]. There could also be criticism that patients are deprived of a chance to achieve longer survival by using only the standardized criteria. Therefore, LDLT should be considered even in patients with advanced HCC if there are no other effective treatment options and patients are expected to benefit from LT, and if a donor shows strong desire for living donation after being informed about the expected survival and risk after LT.

Prognostic biologic factors of LT for HCC

Although the conventional selection criteria for LT for HCC, including the Milan and UCSF criteria, are based solely on the size and number of tumors, other factors have been proven to predict HCC recurrence after LT. Microvascular invasion and poorly differentiated HCC are the well-known risk factors for post-LT recurrence [18–19,43–45]. The Toronto group suggested that poorly differentiated HCC on biopsy should be excluded for LT because tumor differentiation may be a more important predictor of biological behavior than

tumor size, number or even microvascular invasion [45]. However, these are not useful as factors for selection criteria because they can only be assessed postoperatively or through an invasive biopsy procedure [46–48].

We previously reported on the significant preoperative biological factors such as AFP, PIVKA-II, and 18F-FDG positron emission tomography (PET) positivity [15–17,49–51]. AFP, a historical tumor marker of HCC, is also associated with early recurrence after resection [52,53,54]. Preoperative serum PIVKA-II level was recently reported as a possible indicator of microvascular invasion in HCC [55,56,57]. PET can represent the differentiation of HCC [58]. Combination of these biological factors might predict HCC recurrence better than the conventional criteria based on the size and number of tumors. In fact, many Asian transplant centers have already adopted biological factors when making their new selection criteria for LT for HCC [9,10,12]. The Kyoto group of Japan expanded the number and size of tumors to ten or less tumors ≤ 5 cm in diameter but limited the serum PIVKA-II level to ≤ 400 mAU/ml for LDLT for HCC [10]. They reported that the 5-year overall and disease-free survival rates were 86.7 and 95.1% respectively in patients who met their new criteria [10]. Kim *et al.* [59] of Korea defined the new expanded criteria as less than or equal to seven tumors, a maximum tumor size ≤ 6 cm, and serum AFP level ≤ 1000 ng/ml to minimize the risk of HCC recurrence. According to their analysis, the 5-year disease-free survival rate of patients within their new criteria was 90.0% [59].

Our retrospective analysis of 113 patients who underwent LDLT for HCC showed that the serum AFP level, serum PIVKA-II level and 18F-FDG PET positivity were statistically significant variables for predicting HCC recurrence after LT [15]. Even among patients within the Milan criteria, all patients with three high risk biologic factors (AFP ≥ 100 ng/ml, PIVKA-II ≥ 100 mAU/ml, positive PET) had HCC recurrence. On the other hand, among patients beyond the Milan criteria but without high risk biologic factors (AFP < 100 ng/ml, PIVKA-II < 100 mAU/ml, negative PET) only 11.1% experienced HCC recurrence post-LT [15]. Preoperative serum AFP level, PIVKA-II level and PET positivity of the tumor play a significant role in predicting HCC recurrence after LT across the Milan criteria. Tumor biologic factors offer the possibility to overcome the limitation

of conventional selection criteria. Therefore it is clear that the biologic factors of HCC should be used to identify suitable candidates for LT although the type of the most useful factor and its cut-off value has not yet been completely established. HCC patients with high risk tumor biology across the Milan criteria must be considered as candidates for LT with caution. In addition, we propose that HCC patients with favorable tumor biology should not be excluded from LT, especially from LDLT, simply because they are beyond the Milan criteria [60].

Seoul National University Hospital experience of LDLT for far-advanced HCC

LDLT is one of the important treatment modalities for HCC in Asian countries. LDLT has been increasingly performed for HCC and recently it accounted for more than 60% of adult LDLT at Seoul National University Hospital (Figure 1). Because a living donor liver graft is dedicated to only one recipient, its indication can be expanded. The question is ‘what is the minimal estimated survival to balance donor risk?’ Some centers still stick to the expanded selection references that are estimated to yield a 5-year survival rate of approximately 50% [60]. However, there was no criterion to predict HCC recurrence exactly. In addition, LDLT is very occasionally not performed by the physicians due to the Korean culture of strong family affection when a donor earnestly requests for it after he or she is informed of the expected survival and potential risks. Therefore, the proportion of patients with advanced HCC undergoing LDLT is inevitably increasing and experiences of LDLT for advanced HCC have accumulated in our center.

Approximately 20% of adult LDLT was recently performed for HCC beyond the Milan criteria in our center [15]. Five-year overall and disease-free survival rates after LDLT were 65.4 and 59.1% respectively for patients beyond the Milan criteria, which were acceptable although significantly worse than those for patients within the Milan criteria (Figure 2) [15]. In addition, we found that the preoperative serum AFP level, PIVKA-II level and PET positivity of the tumor were important prognostic factors in patients across the Milan criteria. Based on these results, we experimentally and very selectively expanded the indication of LDLT for HCC to far-advanced HCC; HCC > 10 cm in diameter, more than ten in number

Figure 1. Annual number of cases of adult living donor liver transplantation at Seoul National University Hospital. The incidence of adult living donor liver transplantation for hepatocellular carcinoma has been increasing, recently accounting for more than 60% of adult living donor liver transplantation in Seoul National University Hospital.
HCC: Hepatocellular carcinoma; LT: Liver transplantation.

or with portal vein tumor thrombus (PVTT) preoperatively [60–61]. Twenty-nine patients underwent LDLT for far-advanced HCC at our center from January 2003 to February 2013. As expected, the post-transplant outcomes of patients with far-advanced HCC were poorer than those of patients who meet the Milan criteria. The 1-, 3- and 5-year actuarial survival rates were 75.9, 46.4 and 31.3% respectively. The corresponding disease-free survival rates were 44.8, 28.4 and 28.4%. Nine patients did not experience HCC recurrence during the median follow-up period of 36.4 (10.3–111.2) months. The 3-year disease-free survival rate of patients with PVTT was 34.3%, which was similar to that of patients without PVTT (21.4%, $p = 0.378$). According to the type of PVTT [62], patients with type I or II PVTT had a lower recurrence rate than patients with type III or IV PVTT, which was also statistically insignificant (61.1 vs 80.0%, $p = 0.128$). In the multivariate analysis, only pre-transplant serum AFP level >200 ng/ml was a significant

risk factor for HCC recurrence after LT (HR 5.483, $p = 0.001$). Although all patients with PVTT and a pre-transplant serum AFP level >200 ng/ml had HCC recurrence in 2 years after LT, patients with PVTT but AFP ≤ 200 ng/ml had excellent overall and disease-free survival rates after LT (87.5 and 65.6% at 3 years post LT, respectively) (Figure 3). A 46-year-old male underwent LDLT for huge HCC with type II PVTT at our center. He had HBV-related liver cirrhosis for a long time and eventually developed HCC in segment 6. The tumor could not be controlled in spite of one ethanol injection and two transarterial chemoembolization sessions, and it progressed to invade the portal vein. Preoperative serum AFP and PIVKA-II levels were low (8.8 ng/ml and 37 nAU/ml respectively). The tumor was single and its size was 11.0 cm pathologically. Fortunately, he has been tumor-free for more than 3 years at the time of writing this article. We believe he derived significant benefit from LDLT. This presented case shows the necessity

Figure 2. Five-year survivals of patients with hepatocellular carcinoma after living donor liver transplantation according to the Milan criteria. (A) Five-year overall and (B) disease-free survival rates after living donor liver transplantation were 65.4 and 59.1%, respectively, for patients beyond the Milan criteria, which were acceptable although significantly worse than those for patients within the Milan criteria.

HCC: Hepatocellular carcinoma; LDLT: Living donor liver transplant.

Figure 3. Survival of patients with portal vein tumor thrombus after living donor liver transplantation. Patients with portal vein tumor thrombus (PVTT) but with pre-transplant serum AFP level ≤ 200 ng/ml had acceptable overall (A) and disease-free survival rates (B) after living donor liver transplantation (87.5 and 65.6% at 3-years post-LT, respectively).

LDLT: Living donor liver transplant.

for new criteria. Based on our experience, we concluded that LDLT can be performed even in patients with far-advanced HCC including PVTT, resulting in satisfactory outcomes if tumor biology is favorable.

Treatment of HCC recurrence after LT

HCC recurrence is one of the most serious complications after LT; it rapidly progresses under the immunocompromised state and leads to death in most cases even when aggressive and combined therapeutic approaches are applied [63–67], and this is the reason why a large expansion of the selection criteria for LT for HCC is difficult. In some patients, surgical resection of intra- and extra-hepatic tumors can effectively prolong their lives after recurrence [24,65,68–69]. Unfortunately the surgical approach is often not possible due to extended tumor dissemination [63,65–66]. Patients with HCC recurrence not amenable to surgical resection have very limited therapeutic options due to the lack of efficacy of conventional cytotoxic chemotherapy [70]. Once tumor progression goes beyond treatment control, dismal prognosis invariably occurs.

Currently, there are two increasing possibilities for the management of HCC recurrence after LT. One possibility is the mTOR inhibitor-based immunosuppression. The mTOR inhibitor, a newly introduced immunosuppressant, has antineoplastic action and may reduce HCC recurrence rates [71]. Some retrospective studies suggested that sirolimus-based immunosuppression may be associated with delayed tumor recurrence compared with tacrolimus-based regimens [72–73]. Switching to an mTOR inhibitor after recurrence can also be helpful. Although there are only a few reports showing the efficacy of immunosuppressant conversion to an mTOR inhibitor in HCC recurrence after LT, the results were encouraging [74–76]. Given the overall poor prognosis of HCC recurrence and the limited systemic treatment options, switching to an immunosuppressive agent with intrinsic antiproliferative capability seems attractive and an obvious possibility [77].

The other possibility is sorafenib. Sorafenib is a multi-tyrosine kinase and angiogenesis inhibitor with activity against VEGFR2, PDGFR, *c-Kit* receptors, *b-RAF*, and *p38* signal transduction pathways, which are involved in HCC pathogenesis [77–78]. In patients with advanced HCC and compensated liver cirrhosis, sorafenib has been shown to improve survival by

approximately 3 months [79]. In addition, several groups have also reported survival benefits of sorafenib treatment in patients with HCC recurrence after LT based on their retrospective experience, in most cases in combination with mTOR inhibitor-based immunosuppression [75–76,80–81]. According to a case–control study by Sposito *et al.* [80], median survival following recurrence in the sorafenib group was significantly longer than that in the non-sorafenib group (21.3 vs 11.8 months, hazard ratio = 5.2, $p = 0.0009$). Furthermore, a few cases with complete remission after sorafenib treatment have also been reported [82,83]. Unfortunately there are no randomized controlled trials with these two promising agents, mTOR inhibitor and sorafenib. Further studies are required to identify whether these agents are effective for HCC recurrence after LT.

We experienced a case of post-transplant HCC recurrence treated by repeat LT. The patient was a 60-year-old male. He had far-advanced HCC and underwent LDLT from his son. Preoperative serum AFP level was <5 ng/ml. The number of HCCs was more than ten and the maximal tumor size on the explanted liver was 2.4 cm. However, HCC recurred 13.3 months after LT. Four recurrent tumors without extra-hepatic metastasis were found in the liver. The patient and his family took a decision in favor of re-LT and he underwent re-LT 4.5 months later. Serum AFP level was <5 ng/ml at the time of re-LT. The result of re-LT was excellent without the use of an mTOR inhibitor and sorafenib despite exceeding the Milan criteria even at the time of re-LT. He has been tumor-free for approximately 10 years until now after undergoing two LTs. Therefore, HCC recurrence after LT is not a catastrophic complication any more. A combination of surgical approach, mTOR inhibitor and sorafenib could provide long-term survival in patients even after HCC recurrence.

Conclusion

In conclusion, the size and number of tumors are insufficient to predict HCC recurrence after LT. Biological factors such as preoperative serum AFP level, PIVKA-II level, and 18F-FDG PET positivity of the tumor can play an important role in predicting HCC recurrence across the Milan criteria in LDLT. Patients with far-advanced HCC have poor prognosis after LT. Nonetheless, we consider LDLT as a treatment option for them because: many patients with far-advanced HCC

have few better treatment options than LT; the indication of LDLT can be expanded because a liver graft is dedicated to only one recipient; even advanced HCC might not recur if it has favorable tumor biology; and combination of surgical resection, mTOR inhibitor and systemic therapy with sorafenib could provide long-term survival even after post-transplant HCC recurrence. Therefore, we are expanding the indication of LDLT to patients with far-advanced HCC in the following selected situations: there are no other effective treatment options, patients are expected to benefit from LT (tumor biology is favorable), and the expected survival and donor risk are fully understood by both the recipient and the donor. Currently, the only absolute contraindication for LDLT at our center is extra-hepatic metastasis. However, our conclusion was only based on retrospective experiences and the sample size was too small to draw a persuasive conclusion. Thus, our results should be validated by worldwide major LDLT centers. We are now performing a Korean multicenter study to establish safe and effective selection criteria for LDLT.

Future perspective

LDLT for advanced HCC could be criticized because of the expected poor prognosis and donor risk. Some patients with far-advanced HCC, however, do not have HCC recurrence and derive significant benefit from LT. As observed during our experience, the result is influenced significantly by tumor biology of HCC. Therefore, it is important to identify effective markers for predicting post-LT recurrence and for deciding the cut-off value

of these markers. Most Asian LDLT centers would have some experience of LT for advanced HCC. We look forward to the co-operation of the Asian LDLT study group regarding this work, which could help in developing new reliable criteria for LT for advanced HCC from their large data.

Treatment of HCC recurrence after LT will become a significant issue in the coming years. Although the most effective treatment of HCC recurrence after LT is surgical resection, many recurrent cases are not amenable to surgical approaches. There are several reports showing improved survival after treatment with mTOR inhibitors and sorafenib. However, to establish the efficacy and safety of these treatments, further studies are needed, including large cohort studies or prospective randomized trials. These medications are now being used in many LT centers worldwide. In the near future, the results of clinical studies will provide a guideline on therapies for managing recurrent HCC. In addition, the expansion of criteria for LT to advanced HCC could be more strongly supported by the established efficacy of mTOR inhibitors and sorafenib in preventing and treating HCC recurrence after LT.

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