



Living-donor liver transplantation for hepatocellular carcinoma in Japan and Korea

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Introduction

Liver transplantation is now one of established therapeutic options for patients with hepatocellular carcinoma (HCC) and decompensated cirrhosis (1). Liver transplantation is a theoretically ideal therapeutic modality because both the tumor and the underlying disease of the liver can be treated at the same time (2).

When tumors are in an early stage, liver transplantation is effective (3). Mazzaferro *et al.* (4) proposed criteria for tumors in a liver transplant setting: up to three tumors of ≤ 3 cm in diameter or a single tumor ≤ 5 cm in diameter, no major vascular invasion, and/or extrahepatic lesions based on imaging studies. Under these criteria, a 4-year survival of 75% and a recurrence-free survival of 83% were obtained. Especially in deceased donor liver transplantation (DDLT), many centers around the world have used these criteria to select candidates for liver transplantation due to HCC. The criteria are considered too strict, however, preventing some potential liver transplant candidates with HCC from getting a second chance (5).

Newer criteria have now been proposed mainly for HCC patients undergoing living donor liver transplantation (LDLT) in Korea and Japan. LDLT can be performed when a donor having a firm relationship with the patient volunteers to donate. Under these conditions, the criteria for selecting candidates with HCC for LDLT can be somewhat expanded from the Milan criteria.

Korean and Japanese perspectives of LDLT for HCC

Most LDLT centers in Korea and Japan currently apply their own selection criteria for LDLT to patients with HCC, which have been expanded from the Milan criteria (6). The criteria basically include the number and maximum size of the HCC lesions as determined by imaging studies. The Tokyo criteria allow up to five tumors with a maximum diameter of 5 cm (6). In their series, recurrence-free survival was comparable to that when the expanded selection criteria were adopted. Lee *et al.* at the Asan Medical Center proposed the following criteria: up to five tumors with a maximum tumor diameter of 6 cm. Again, recurrence-free survival was comparable to that of patients within the Milan criteria. The Asan and Tokyo criteria have slightly extended the Milan criteria to obtain results comparable to those under the Milan criteria (7).

Other centers in Korea and Japan have proposed different criteria using tumor markers. The Kyoto group (8) proposed mildly expanded criteria in the LDLT setting, i.e., up to 10 tumors, each with a maximum diameter of 5 cm, and des-gamma-carboxy prothrombin levels ≤ 400 mAU/mL. The Kyushu group criteria removed the limitation of tumor number (9), but kept the maximum tumor diameter of 5 cm and reduced the serum des-gamma-carboxy prothrombin level to ≤ 300 mAU/mL. The 5-year recurrence-free survival

rate under these criteria is 80%, and that under the Milan criteria is 96%.

It is clear that size and number of HCC tumors may be insufficient parameters for predicting HCC recurrence. The selection criteria for transplant patients with HCC have shifted from morphologic criteria (i.e., tumor size and number) to criteria combining biologic, histologic, and morphologic characteristics. The Samsung group in Korea (10) added alpha-fetoprotein levels. Their criteria comprise up to 7 tumors, maximum tumor diameter 6 cm, and serum alpha-fetoprotein level $\leq 1,000$ ng/mL. Under these criteria, the 5-year recurrence-free survival rate is 84%. The criteria applied at Kyushu and Samsung are acceptable in the LDLT setting, although the HCC recurrence rates after transplantation are higher than those expected when the Milan criteria are applied. Seoul National University now selects patients not based on the size and number of tumors, but on alpha-fetoprotein level (≤ 200 ng/mL) and negative results of fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) (11). The National Cancer Center of Korea (12) has proposed new criteria comprising the sum diameter of all tumors up to 10 cm and negative FDG-PET findings.

Role of LDLT for HCC patients and expected survival after LDLT

LDLT is more popular than DDLT in Korea and Japan, as in other Asian countries except for mainland China, in contrast to Western countries (13). Liver grafts in LDLT are not obtained from public resources and thus need not be limited by the organ allocation system (14). In LDLT, not only the postoperative survival probability of the liver graft but also the donor's preferences should be considered. Donor morbidity still remains a significant risk. Recent data indicate that the risk of death and severe complications (Clavien grade $\geq 3b$) associated with the donor operation are as high as 0.3% and 2%, respectively (15). LDLT should be performed by transplantation experts at high-volume centers of liver resection and DDLT.

How is the minimal acceptable survival in LDLT set and defined? The target outcome is a 5-year survival rate ranging from 50% to 60% (16). It might not be easy for (transplant) hepatologists and physicians to deny a request to perform LDLT if a donor wishes to provide the graft as the curative treatment for the patient (3). It is important to maintain a balance between recipient benefit and donor

risk (17). As major complications in living donors can be reduced by meticulous surgical techniques, LDLT should be performed in high-volume liver resection and LDLT centers (14) with extensive surgical expertise.

Conclusions

LDLT accounts for the majority of liver transplantation in Korea and Japan. Considering that liver grafts from living donors cannot be obtained from public resources, the patient survival probability and donation will of the donor should be considered. The selection criteria of LDLT patients for HCC can be expanded from the Milan criteria composed of morphologic and biologic parameters of the HCC tumors. To establish a consensus on the alternative criteria, however, additional studies are necessary.

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Footnote

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