Editorial

# Resection versus transplantation for hepatocellular carcinoma exceeding Milan criteria within increasing donor shortage

**Kuniya Tanaka**

Department of Surgery, Division of Hepato-Biliary-Pancreatic Surgery, Teikyo University Chiba Medical Center, Chiba, Japan

*Correspondence to:* Kuniya Tanaka, MD. Department of Surgery, Division of Hepato-Biliary-Pancreatic Surgery, Teikyo University Chiba Medical Center, 3426-3 Anesaki, Ichihara, Chiba, 299-0111, Japan. Email: U17-92TS@med.teikyo-u.ac.jp.

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Until establishment of the Milan criteria in 1996, long-term survival in many hepatocellular carcinoma (HCC) patients receiving liver transplants was elusive, raising questions about practicality of transplantation in these patients (1). Subsequently, strict adherence to the criteria led to survival roughly equivalent to that of non-tumor patients undergoing liver transplantation, so HCC patients represented equally sound organ utilization and could be included in allocation algorithms (2). In many European studies, 5-year survival after liver transplantation for patients with HCC within Milan criteria ranged from 71% to 75% (2-5). Unfortunately, up to 70% of patients with HCC are diagnosed at advanced stages of disease (6), and are not suitable transplantation candidates by Milan criteria. For most of these patients, current treatment options offer little chance of cure (7,8). This had led some authors to extend transplantation to patients with tumors exceeding Milan criteria.

The Milan criteria were based on clinical experience, so they might not necessarily establish ideal cut-off points. Many surgeons have expanded criteria for liver transplantation in HCC and reported acceptable survival. Overall and disease-free survival similar to those of patients within Milan criteria were obtained in transplanted HCC patients meeting University of California, San Francisco (UCSF) criteria (single tumors ≤6.5 cm in diameter, or no more than 3 lesions ≤4.5 cm in diameter and ≤8 cm in total diameter) (9). The Tokyo criteria (5 nodules with maximum diameter of 5 cm) (10), Navarra criteria (single tumors ≤6 cm or 2–3 nodules ≤5 cm) (11), Asan criteria (≤6 tumors, all ≤5 cm) (12), Valencia criteria (1–3 tumors ≤5 cm with combined size ≤10 cm) (13), and "up-to-seven" criteria (diameter of largest tumor in cm plus number of tumors ≤7) (14) each identified HCC patients beyond the Milan criteria who could benefit from transplantation without worsening survival outcome. These criteria rely mostly on tumor size and number. Other proposed criteria for tumors beyond Milan include markers of tumor behavior, such as the Kyoto criteria (≤10 tumors all ≤5 cm in diameter, plus PIVKA-II ≤400 mAU/mL) (15), the Hangzhou criteria (total diameter ≤8 cm, or total diameter >8 cm, plus histopathologic grade I or II and α-fetoprotein ≤400 ng/mL) (16), and the Toronto criteria (biopsy-confirmed moderate-to-high differentiation and no severe systemic symptoms) (17).

In 2002, the transplantation community assigned an intentionally high model for end-stage liver disease (MELD) score to HCC patients when they were listed, and increased that score every 3 months (MELD elevator), aiming for equal rates of wait-list death or dropout between patients with and without HCC (HCC-MELD exception). However, because of lower wait-list mortality and dropout rates in HCC patients than in non-HCC patients, prioritization and allocation rules have changed drastically. When the MELD-based system was introduced, the MELD score was 29 points for tumors that were United Network

for Organ Sharing (UNOS) stage T2; this was reduced to 24 points in 2003 and 22 in 2005. Additional changes in 2015 included an "HCC Delay" policy requiring a 6-month delay after listing for transplantation before assigning an exception MELD score of 28, and a "Cap HCC" policy that capped scheduled progression on the "MELD elevator" at a maximum score of 34. These policies aimed to slightly reduce access to transplantation in HCC patients with MELD score <28 and reduce disparities between HCC and non-HCC patients with MELD score ≥35. These complexities reflect the difficulties resulting from the organ shortage and from liver transplant allocation being driven in recent years by HCC at the expense of non-HCC patients.

Discrepancies between imaging and pathology make assessment more complicated when pathology is included among transplantation criteria. A previous study found that only 44% of tumors were staged accurately by pretransplant imaging (18), with up to one-third of patients reportedly misclassified as within or beyond Milan criteria based on imaging (17). Further, after downstaging by loco-regional therapy followed by liver transplantation, 15% of patients were found pathologically to exceed T2 tumor stage despite being downstaged to T2 criteria according to imaging and thereby made eligible for transplantation (19).

Zaydfudim *et al.* (20) reported that in five major specialized centers, overall and disease-free survivals both were greater after tumor downstaging and transplantation than resection. Downstaging of HCC to within Milan criteria seems preferable to simply expanding tumor size limits. Successful downstaging of HCC to within UNOS T2 criteria (Milan criteria) was associated with a low rate of HCC recurrence and excellent post-transplant survival, comparable to patients meeting T2 criteria without downstaging (21). Theoretically, downstaging treatments allow selection of tumors with more favorable biology that respond to these treatments and subsequent ones if needed, with patients therefore doing better following liver transplantation. On the other hand, long-term results obtained by downstaging with transplantation might be similar to those obtained by downstaging with resection.

Inferior results of resection compared with transplantation are easy to understand irrespective of the effect of downstaging pretreatment considering the possibility of microvascular invasion in the nonresected portion of the liver or emergence of *de novo* tumors from cirrhotic liver tissue containing premalignant clonal abnormalities that might resist pretreatments such as transarterial chemoembolization (TACE). Nonetheless, the conclusion reached by Zaydfudim *et al.* (20) was somewhat different from the earlier report of Majno *et al.* (22), which advocated use of loco-regional therapy such as TACE to reduce the volume of HCC, thus facilitating either resection or transplantation. The fundamental principle behind considering downstaging in transplantation decisions is to select a subset of tumors with more favorable biology so that patients are more likely to respond to treatment and do well after transplantation, but they might also do well after resection. Therefore, downstaging may not necessarily argue for transplantation to include patients with HCC beyond Milan criteria who receive pretreatment, even if long-term results of transplantation generally are superior to those of resection. Long-term survival of HCC patients must be weighed against that of non-HCC transplant patients, considering the increasing donor shortage. In addition, difficulties exist in determining how loco-regional treatments and patient response to such treatments should affect prioritization scores. Expanding indications for liver transplantation using downstaging pretreatment could only lengthen the waiting list by adding patients at increased risk for eventual dropout, thus compromising the intention-to-treat outcome of all HCC patients (23).

Transplantation for HCC beyond Milan criteria would cause significant harm to non-HCC patients on the waiting list. According to one report, transplantation criteria in HCC patients could be expanded only when the 5-year posttransplant survival rate exceeds 61%, in order to avoid undue harm to other patients (24). When reported survival rates remain below this threshold, expanding the Milan criteria at any individual institution may be premature. Since most centers currently report survival rates below 61%, this also would appear to apply at a national or international level. From the standpoint of organs scarcity, a more aggressive approach to transplantation in these patents may be justified only in regions with less severe organ shortage or in case of living-donor transplantation.

Expanding transplantation for HCC beyond Milan criteria also may be economically unsound. Even in HCC patients within Milan criteria and classified as Child-Pugh A or B with respect to cirrhosis, liver resection is considered more cost-effective than cadaveric transplantation (25). While recurrence rates in transplantation often are lower than in resection, transplantation may tax resources in many countries. Liver transplantation also requires long-term immune suppression, which carries additional risks and significant lifetime costs. If cadaveric liver transplantation-related 5-year cumulative survival in HCC could be

 

improved to exceed 87.6% for the US or 84.9% for Singapore, transplantation reportedly would be more cost-effective than resection (25). On the other hand, if 5-year cumulative survival after cadaveric transplantation is less than 83% in the US or 79% in Singapore, resection is more cost-effective than transplantation even with the most pessimistic post-resection 5-year cumulative recurrence rate and annual mortality risk of recurrent HCC (25). While some specialized centers report 5-year survivals exceeding 80%, reports from large registries show 5-year survival rates after liver transplantation for HCC ranging from 60% to 65%, even within the Milan criteria (26).

In conclusion, post-transplant survivals exceeding those with resection in patients whose tumors exceed Milan criteria could lead to expanded indications for transplantation in HCC, but the needs of non-HCC patients also need consideration given the donor shortage. In the future, new biologic survival predictors may improve accuracy of prognostication and successfully expand criteria for liver transplantation in HCC beyond Milan.

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## Footnote

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