Milan criteria and its expansions in liver transplantation for hepatocellular carcinoma

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Mazzaferro *et al.* reported that liver transplantation was an effective treatment for small, unresectable hepatocellular carcinoma (HCC) in patients with cirrhosis in 1996 (1). This seminal publication from Milan, Italy, set criteria (single tumors ≤5 cm in diameter or no more than three tumors ≤3 cm in diameter) for OLT in patients with HCC, which was known as "Milan criteria". The 5 cm was the generally accepted cutoff for small intrahepatic tumors, which was used in patient selection for the studies before Mazzaferro's report. In the report of Bismuth, patients with no more than three tumors and ≤3 cm in diameter were considered eligible for transplantation (2). Thus instead of a result of mathematic model, Milan criteria was an expansion of clinical criteria for HCC, based on clinical experiences.

After Milan criteria was initially employed in liver transplantation for HCC, better outcomes of liver transplantation were observed. Small, single-center, European studies have suggested that 5-year survival after liver transplantation for patients with HCC within Milan criteria ranged from 71–75% (1,3-5). Milan criteria became wide accepted criteria for HCC in liver transplantation. At the same time, liver transplantation has become an effective treatment for HCC.

However, the selection criteria of liver transplantation for HCC relies mostly on tumor size and number and all these criteria were originally from clinical experiences. It is not clear whether these criteria establish ideal cut-off points. Many studies have shown that acceptable survival can be achieved after extending the size and number of tumors. Navarra criteria (single tumors ≤6 cm or 2–3 nodules ≤5 cm) and Asan criteria (≤6 tumors all ≤5 cm in diameter) were expansions of Milan criteria, both of which identified additional HCC patients who could benefit from liver transplantation, without worsening the results (6,7). Then, the total tumor diameter or volume (8) was employed as an essential issue. Patients with HCC meeting the 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 total tumor diameter ≤8 cm) were reported to have similar overall survival (OS) and disease-free survival (DFS) survival rates at 5 years in comparison with Milan criteria (9-12). Mazzaferro *et al.* also conducted a large sample retrospective study in 2007 (13). The 283 patients within the up-to-seven criteria [the sum of the size of the largest tumor (in cm) and the number of tumors ≤7] achieved a 5-year OS of 71.2% (13). A study from Spain reported that patients beyond Milan criteria but under Valencia criteria (1–3 tumors ≤5 cm and cumulative tumor burden ≤10 cm) had a similar 5-year OS with patients under Milan criteria (14).

When these criteria were applied to clinical practice, several problems raised. The discrepancy between imaging and pathology made assessment more complicated. First, HCCs may be understaged or overstaged before pathology is reviewed (15). Up to one third of patients were reported to be misclassified as being within or beyond the Milan criteria based on imaging (15). Second, how to stage HCCs after hepatectomy or neoadjuvant therapies is not clear. Downstaging reduces the number and total tumor volume of HCC and makes them meeting Milan or expended criteria. It was reported that when Milan criteria was employed, there was no significant difference in graft survival between patients with history hepatectomy or not (16). Similarly, data from UCSF showed that 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, which was comparable to those meeting T2 criteria without downstaging (16). Further investigations are needed to confirm the efficacy of liver transplantation after downstaging in the subgroup of expanded criteria.

Factors that correlate with tumor behaviors may be more reliable in predicting the prognosis of liver transplantation (17). Circulating biomarkers such as alpha-fetoprotein (AFP) and vitamin K absence or antagonist-II (PIVKA-II) (18,19) were employed in pre-transplantation assessment. The AFP level has been shown to correlate with the outcomes of surgical treatment of HCC and its independent prognostic value was also found in liver transplantation (20). Duvoux *et al.* reported that prognostic model for predicting recurrence in liver transplant candidates with HCC was improved after AFP was included (8,20-22). Serum AFP level has already been included in Hangzhou criteria and been used in the prognostic stratification of transplant candidates for HCC (22). In total, 100 and 1,000 ng/mL were used as cutoff values of AFP in some prognostic studies (20-23). Base on the multivariate analysis of risk factors for HCC recurrence, PIVKA-II was included by Kyoto criteria (≤10 tumors all ≤5 cm in diameter and PIVKA-II ≤400 mAU/mL) (18). In this study, patients whose HCC exceeded the Milan criteria but displayed ≤10 tumors all ≤5 cm in diameter achieved a similar 5-year tumor recurrence rate with patients with HCC under Milan criteria (18). PIVKA-II ≤400 mAU/mL was another independent prognostic factor of HCC recurrence (18,24). Thus Kyoto criteria were set up as combination of them.

Besides these non-invasive examinations, biopsy may represent more information of tumor behaviors. The histological finding of microvascular invasion, the grade of tumor differentiation and the result of immunohistochemical staining for biomarkers may be helpful to the description of tumor biological behaviors. Rroutine pre-orthotopic liver transplantation tumor grading was suggested in a report from Italy and poorly differentiated HCC (G3) at pre-OLT FNAB was found to correlate with poor prognosis (17). A mandatory percutaneous tumor biopsy of the largest lesion was conducted in the Toronto General Hospital, to determine the differentiation of HCC (15). In this study, patients with HCC exceeding Milan criteria were also selected for transplantation, if biopsy confirmed moderate-high differentiation, as well as no severe symptoms attributable to HCC or vascular invasion existed (15,23). The protocol using a biopsy to exclude poorly differentiated tumors achieved excellent survival rates after liver transplantation (15).

Many reports found microvascular invasion was an independent prognostic factor of poor survival after liver transplantation (14,25,26). Similarly, biomarkers such as vascular endothelial growth factor (VEGF) (27) and Ki67 (28) are also found correlated with HCC recurrence after liver transplantation. However microvascular invasion, VEGF and Ki67 were not involved in any criteria for patient selection before transplantation. Besides, more clinical studies should be conducted to confirm the practical significance of the biomarkers.

Though expanded criteria were supported by many studies, the long-term survival for patients with HCC beyond Milan criteria may be compromised. "No statistical significant found between survivals" can also be attributed to the small sample sizes or the limitation of statistical methodology. The results of many studies were interpreted as "compatible" or "acceptable", based on the presentation of 5-year OS and DFS. However another question arises, what are the acceptable 5-year OS and DFS. Regarding the increasing donor shortage, the 5-year OS and DFS of HCC patients must be balanced with non-HCC transplanted patients. Thus, it seems more complicated to find the ideal cutoffs of tumor size, number and other markers.

Initially, a common agreement in the transplant community was that patients should only be listed when the 5-year survival probability after LT exceeded 50% (29). When compared with non-transplanted HCC patients, 50% seemed acceptable. However, the benefit of patients with and without HCC should be balanced in the context of donor shortage. The United Network for Organ Sharing (UNOS) adopted the Model for End-Stage Liver Disease (MELD) score to determine the priority for liver transplantation. The MELD score was used to predict mortality without liver transplantation, which was decided by serum bilirubin, creatinine and international normalized ratio for prothrombin time (INR). Under this system, patients with the highest MELD scores, the highest predicted mortality without liver transplantation will receive transplantation first. Because patients with HCC under Milan criteria may have relatively low MELD scores and high survival probabilities, priority scores are allowed to them. So that liver transplantation could be conducted before tumors grow beyond the Milan criteria. Initially, 24 points were assigned to stage 1 tumors

(1 nodule <2 cm) and 29 points to stage 2 tumors (1 nodule 2–5 cm or 2 or 3 nodules each <3 cm) (30). A 6-fold increase in the proportion of recipients with HCC was found (31). Then revised versions were used from April 2003 to March 2005. Finally no point was assigned to stage 1 tumors and 22 points were assigned to stage 2 tumors (30). From 2002 to 2007, patients with an "HCC-MELD-exception" had similar survival to patients without HCC (30). However, patients with larger tumors (3–5 cm) had poor posttransplantation survival compared with non-HCC patients with similar MELD scores (30). Patients with HCC >3 cm, AFP level >455 ng/mL, or MELD score >20 have particularly poor posttransplantation survival (30).

How and when to give priority to patients with HCC beyond Milan criteria is not well studied. Certain regions of UNOS have developed region-specific policies to assign exception point to tumors within UCSF criteria. However, such policies have not been accepted formally by UNOS. A study from University of Pennsylvania suggested to consider transplantation for patients with HCC beyond Milan criteria and to prioritize certain candidates because of their higher risk of waitlist mortality (31). In the study of University of Michigan Health System, a Markov model was created to compare the survival benefit of liver transplantation for a patient with HCC beyond Milan criteria versus the harm caused to other patients on the waiting list. In this study, transplantation for HCC beyond Milan criteria would cause significant harm to the other patients on the waiting list. Based on the result generated from this Markov model, criteria of HCC can only be expanded when the 5-year posttransplant survival rate is more than 61%, so that to outweigh the harm to other patients (32). When most reported survival rates below this threshold, it may be premature to expand Milan criteria (32). This work gives a bottom line of 5-year survival after criteria expansion and can be used as a measurement for the practical significance of criteria for HCC patient selection. However this bottom line decided by many factors which will change with time and country, such as waiting list size, organ arriving per year, waiting list mortality, median time-to-transplant, proportion of high MELD score patients, posttransplant survival and so on (32).

In addition to the benefit of patient survival, the cost-effectiveness of liver resection and cadaveric liver transplantation was also studied by another Markov cohort model. The analysis was conducted in different geographical cost settings, including the USA, Switzerland and Singapore (33). The incremental cost-effectiveness ratio (ICER) of cadaveric liver transplantation versus liver resection (ranged from $111,821/QALY to $156,300/QALY) was above thresholds for cost-effectiveness in all three countries (33). Therefore, liver resection is more cost-effective than cadaveric liver transplantation in patients with HCC within the Milan criteria and Child-Pugh A/B cirrhosis (33).

A great deal of clinical researches may be needed to introduce any expanded criteria into clinical patient selection. All these researches would be limited by the small number of patients transplanted for HCC beyond Milan criteria and under expanded criteria. After balanced with the harm to non-HCC patients, the benefit of morphological expansion from Milan criteria may be reduced. With the improving of the posttransplant survival of non-HCC patients and the increasing of organ shortage, the clinical importance of the morphological expansion may also be compromised. In conclusion, Milan criteria was still the most widely accepted criteria in reducing posttransplant HCC recurrence and balancing organ allocation between patients with and without HCC, in spite of the transplantation for HCC meeting Milan criteria is not cost-effective.

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Footnote

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