Twenty years of Milan criteria: how far do we go

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the seventh most common cancer worldwide (1). Liver transplantation (LT) is the ideal treatment which can not only remove hepatic tumors but also cure the diseased liver, however, the early results of LT for HCC were disappointing due to high recurrence rate and poor overall survival (2). A prospective cohort study proposed by Mazzaferro *et al.* in 1996 proposed the selection criteria for LT in patient with a single HCC up to 5 cm in size or up to three HCCs no greater than 3 cm in size without vascular invasion or extrahepatic metastasis, which showed 75% overall survival and 83% recurrence-free survival 4 years after LT (3). After the proposal of these well-known Milan criteria (MC), the application of LT in HCC patients with favorable tumor morphology has become widely accepted. In recent years, MC is challenged for its strict limitation in patient selection, and many researchers have tried to modify the MC as expanded criteria in individual institution to allow more HCC patients benefit from LT without hampering their outcomes (4). However, the level of evidence in most expanded criteria is low due to retrospective cohort study and lack of external validation (5). In addition, because the recurrence-free survival and overall survival rate are the matter of debate, the identification of factors closely linked to tumor dissemination from primary HCC after LT for HCC patients seems as crucial as the modification of eligibility criteria exclusively composed of tumor size and number.

What matters most: size, number, or others?

Many institutions use morphological characteristics of HCC in their expanded criteria to select appropriate LT candidates. Yao *et al.* in 2001 reported the well-recognized extended MC, University of California San Francisco (UCSF) criteria, in which patients with a solitary tumor ≤65 mm in diameter, or two or three tumors, each with a diameter ≤45 mm, and a total tumor diameter ≤80 mm showed survival rates of 75% at 5 years (6). Other expanded criteria proposed worldwide also use the size-and-number factor of HCC in pre-LT radiological images as the representative for tumor burden, including "5-5 rule" in Tokyo criteria (tumors up to five nodules with maximum diameter ≤5 cm) (7), "Asan criteria" from South Korea (tumor ≤5 cm in diameter, ≤6 in nodule number) (8), and "Up-to-7 criteria" by Metroticket Investigator Study Group (the sum of tumor number and the size of largest tumor no larger than 7) (9). Five-year overall survival rates of these studies were 75%, 76.3%, and 71.2%, respectively. The basis of these criteria can be interpreted with the association between the diameter of largest nodule and microvascular invasion of HCC which is the expression of aggressive tumor behavior and indicates poor outcomes (10,11). Because macrovascular/microvascular invasion and/or poor differentiation is often discovered in the explant liver with tumor larger than 5 cm (12), it is well recognized to define 5 cm as the limitation of size of largest tumor in Asian institutions.

With regards to the number of the nodules, the acceptable criteria for LT are different among individual institutions. The Kyoto criteria expanded the number of tumors to ten in addition to the largest diameter ≤5 cm and serum des-gamma-carboxy prothrombin (DCP) level ≤400 mAU/mL (13), and the Kyushu group further expanded the criteria by tumor with diameter ≤5 cm and

serum DCP level <300 mAU/mL without restricting tumor number (14). Compared to the number of total nodules, the factors reflecting the entire tumor burden, like the sum of diameter in each tumor and the various biologic markers predicting tumor aggressiveness, correlates more closely to the prognosis and has become incorporated into recent criteria. Toso *et al.* use the data from the Scientific Registry of Transplant Recipients with 6,478 patients in USA to propose new criteria combining the total tumor volume ≤115 cm^3 and alpha-fetoprotein (AFP) level ≤400 ng/mL (15).

The detection of morphologic variables in these expanded criteria depends on the accuracy of preoperative radiologic modality. It is reported there is discrepancy between the explant pathology and preoperative radiology in up to 25% of cases (16). The developments of imaging techniques and modalities during the last two decades have increased the sensitivity and specificity of radiological examinations. More tumors may be detected nowadays than 20 years ago, and it has substantially contributed to the expansion of limitation in radiological variables without impairing survival outcomes.

Besides the morphological and biological factors, the histological features of tumor including microvascular invasion and tumor grade obtained from explant specimen are desirable before LT if applicable, because they are recognized to predict the post-LT recurrence in most studies (5). The Toronto group adopt tumor biopsy in their expanded criteria for tumors beyond MC without any size-and-number limitation to prevent transplant in patient with poorly differentiated tumors (17). However, due to the relatively low sensitivity of biopsy, the heterogeneity of tumor, and the possibility of needle track seeding, tumor biopsy is not recommended to be routinely used in patients considered for LT according to an international consensus report (18). Since it is risky and difficult to get the access to histological features of tumors before LT, noninvasive surrogate markers, including radiological morphology such as fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) (19) and tumor markers such as AFP (15) and DCP (20), have been investigated and reported to improve the performance of recipient selection.

The eligibility of extended criteria

The dual composition of transplantation by donor and recipient makes its eligibility more complicated than other cancer treatment. Expansion of MC recruits more LT candidates with HCC who cannot be treated by locoregional therapy and are excluded from waiting list by conventional criteria due to the tumor burden. On the other hand, the increasing number of HCC patients on the waiting list for deceased donor liver transplantation (DDLT) will certainly lower the chance of LT for those enlisted without malignant diagnosis under the limited donor pool (21). In many Western countries, additional exception point of Model for End-Stage Liver Disease (MELD) score adopted in liver allocation systems is given to HCC patients with potential progression (usually defined as T2 tumor, i.e., solitary HCC ≥2 and <5 cm or 2–3 HCCs <3 cm) to prevent them from dropping out the waiting list due to tumor progression during short waiting period (22). The equality should be evaluated whether the mortality rate of non-HCC patients on the waiting list increases when we try to expand the criteria or to give priority for HCC patients, rather than just considering the results among HCC patients. An analysis using the data from national registry system in USA reported that the post-transplant 5-year survival of patients beyond MC should exceed approximate 61% to outweigh the harm to other candidates without HCC (21). This also indicates that any expanded criteria with 5-year survival rates below 60% is not justified in the DDLT setting.

In Asian countries as well as in Japan, due to severe scarcity of deceased donors, living donor liver transplantation (LDLT) is the mainstream for HCC patients with decompensated liver disease (23). In the LDLT setting, LT for HCC patients beyond the conventional criteria is not restricted by the national allocation system but depends on the case-by-case consideration, including the expectation of patient, survival outcome of recipient, and the will and the safety of donor. It shortens the waiting time of LT candidates with elective preoperative planning. Expanded transplant criteria for LDLT in HCC patients are well adopted in most Asian institutions. However, there is some debate about the higher recurrence rates in LDLT compared with that in DDLT. Studies propose the fast-track feature of LDLT and short observation period before LT may mask the aggressiveness of HCC which leads to higher recurrence. It is also proposed that the rapid regeneration process of partial liver graft and cytokine released might induce the early recurrence of potential microscopic HCC (24). But until now, there is no strong evidence indicating the higher recurrence rates and the inferior survival outcome in LDLT than in DDLT among HCC patients (25). Many institutions in Asian countries have also reported acceptable 5-year survival rates above 70% with expanded criteria in the LDLT setting in comparison with the Western experiences

in the DDLT setting, and warrant the eligibility of LDLT for HCC patients (7,8,13,14).

In contrast to DDLT, expanding selection criteria for HCC patients in the LDLT setting will not influence negatively on other candidate. Degree of expansion for LDLT depends on what level of result we can accept and the expectation of patients. The optimal 5-year survival rate of LT for HCC candidates is above 70%, which is equivalent to that of non-HCC recipient. Nevertheless, as the "metroticket paradigm" describes, we should always be aware of the fact that the longer distance we leave from the conventional criteria; the higher price we should pay by the higher recurrence (9).

Conclusions

The adoption of expanded criteria yielded acceptable survival outcome after 20 years of MC. It needs more studies to clarify the boundary of extension by identifying the prognostic factors closely associated with tumor aggressiveness and predicting early recurrence.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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