Introduction

Liver transplantation (LT) is a curative option for both hepatocellular carcinoma (HCC) and cirrhosis. Twenty years after first Milan criteria (MC) description, they are still identified as the benchmark for selection of patients and set the baseline of survival to achieve (1). When MC was first proposed in 1996, they rapidly became the keystone for the selection of patients with HCC waiting for LT (2). The use of the MC consented to very well selected patients at low risk for post-LT recurrence, consequently obtaining excellent survival rates (3). And yet, different extended criteria have been proposed in the last years all around the world. All of them have an intent to improve the ability to select patients for LT. MC competitors first used only macroscopic criteria and then associated with a biological parameter to find the best selection criteria.

Expanded criteria

Since the MC description, only morphological characteristics of HCC were used as the indication or not to LT. After a few years, other institutions revised these morphological characteristics in their enlarged criteria to cherry pick appropriate LT candidates.

Without doubts, the University of California San Francisco (UCSF) criteria described by Yao et al. in 2001 are one of the most important competitors of MC (4). UCSF reported a survival rate of 75% at five years with the following indications: a single nodule with a maximum diameter of 65 mm, or two or three tumors, each with a maximum diameter of 45 mm, and a sum tumor diameter ≤ 80 mm. On the other hand, because a little number of patients outside MC but within the USCF criteria are candidates for LT, those criteria have not superseded MC in most centers (5).

As a reply to UCSF, Mazzaferro and the Metroticket Investigator Study Group also conducted a large sample retrospective study in 2007. The so-called up-to-seven criteria were described from a cohort of 283 patients with HCC with the following morphological characteristics: the total of the size of the bigger tumor and the number of tumors no larger than 7. In the expanded criteria the overall survival rate achieved at 5-year was 71.2% (6).
The size and number of HCC in the waiting list for LT radiological images were used as well by other enlarged criteria. In the East, the Tokyo criteria named the “5-5 rule” was described for living donor liver transplantation (LDLT) (7). The University of Tokyo guidelines was up to five nodules with a maximum diameter of 5 cm, overall and recurrence-free survival rates at five years after transplantation were 75 and 90%, respectively.

“Asan criteria” from South Korea were proposed by Lee et al. for LDLT as the previous described Tokyo criteria (8). In this case indication for LT is six or fewer tumors with a diameter ≤50 mm. The overall survival rate for patients within the Asan criteria was 76.3% at five years, and the recurrence-free survival rate was 85%.

As previously but from the Catholic Medical Center, Choi et al. push over the limit with for patients with advanced HCC (9). Authors proposed to extend the suitable criteria for LDLT to up to seven tumors with the greatest diameter ≤70 mm. In their series, the overall survival at 5-year was 72%, and the recurrence-free survival was 87%.

A third element

Latterly, different centers have added alternative parameters reflecting the biological comportment of tumors other than the traditional morphological parameters.

Alpha-fetoprotein (AFP) is the largely popular non-invasive biomarker jeopardy element for HCC recurrence after LT.

Using the Scientific Registry of Transplant Recipients database including up to 6,478 patients in the USA, Toso et al. suggest the total tumor volume as the latest predictor of potential HCC recurrence after LT. Authors work out a new composite of criteria associating the entire tumor volume of 115 cm³ or less and a serum AFP level of 400 ng/mL or less (10). The reported in case of patients out of range the MC but inside the new criteria a reasonable recurrence rate (9%) and overall survival rate (75%) at four years after LT. Notwithstanding, the precise measurement of the total tumor volume deriving from tumor diameter is the most limitation of the criteria.

Like the ones described above, to expand the selection criteria, the Samsung Medical Center (SMC) used the serum AFP level too (11). Kim et al. advocated in case of HCC patients with no more than seven tumors ≤6 cm and with serum AFP levels ≤1,000 ng/ml that in those cases LDLT could realistically be performed. Authors obtained an 84% recurrence-free rate at 5-year.

In France, the Liver Transplantation French Study Group publish the “Duvoux Score” predicting the high risk of recurrence post LT according to AFP (12). The score includes a sum of variables: number of nodules (1–3=0 point; ≥4=2 points), largest diameter in cm (≤3=0 point; 3–6=1 point; >6=4 points) and AFP (ng/mL) (≤100=0 point; 100–1,000=2 points, >1,000=3 points). Patients with a score ≤2 points following down-staging treatment will be eligible for registration for liver transplantation.

In Japan, many centers use an alternative tumor marker, des-gamma-carboxy prothrombin (DCP), as well known as a protein induced by vitamin K absence or antagonist II. Waiting LT list serum DCP level was reported as a predictor of the risk of recurrence of HCC after LT as a possible indicator of microvascular invasion. Therefore, both Kyoto and Kyushu groups have at present updated their selection criteria to include pre-LT serum DCP level.

The Kyoto group advanced expanded criteria containing serum DCP level (13). These criteria are defined as the number of HCC nodules to ten in addition to the largest diameter ≤5 cm and serum DCP level ≤400 mAU/mL. The 5-year disease-free and overall survival rates were 93% and 82%, respectively.

Surprisingly, the Kyushu group eliminated the nodule number limitation in the proposed expanded criteria (14). Taketomi et al. included all HCCs with a diameter of ≤5 cm and DCP <300 mAU/mL. The 5-year recurrence-free rate was 80%. Authors advertise the Kyushu criteria as the most potent predictive criteria for post-LT HCC recurrence. However, this last two criteria deriving on Japanese studies were achieved in the setting of LDLT only and needs additional validation in the Western world both in the context of LDLT and post-mortem donor LT (15).

Both Hangzhou and Toronto groups included the HCC biopsy result in their selection criteria.

Hangzhou criteria were defined as total tumor diameter ≤8 cm or total tumor diameter >8 cm, with grade I or II at the histopathologic exam and preoperative AFP level ≤400 ng/mL, simultaneously (16). The 5-year survival rate was 72.3%.

Remarkably, Toronto proposed no limit of number or size of HCC provided that imaging studies excluded vascular invasion; no extra-hepatic disease was observed, and histopathologic exam the HCC was not poorly differentiated (17).

Even though, these two criteria need a pathological staging with a needle biopsy which is a risk factor for both tumor seeding and post-transplant recurrence as well as
possible high bleeding in patients with portal hypertension. The size and the number of nodules within the MC might reflect the outcome of biologically favorable tumors.

**Down-staging**

Tumor biology as differentiation, vascular invasion, and serum AFP has been demonstrated to predict post-transplant recurrence and survival better than the unique morphology parameters. A downstaging therapy selects thanks to the good tumor biology those patients outside standard criteria at presentation but with a high chance of acceptable outcome in case of LT.

Tumor downstaging is a process including enlarged criteria and the results of loco-regional treatment. It is defined as a reduction in the tumor burden using a loco-regional treatment specifically to meet acceptable criteria for LT. A growing number of experiences of the excellent result after downstaging therapy before LT in patients outside MC are now published.

Since a few years ago, portal vein tumoral thrombosis (PVTT) was judged to be an absolute contraindication for LT. Nonetheless, experience with successful LDLT after downstaging for patients with PVTT has been published by the Yonsei University Severance Hospital of Korea (18). Han et al. used a pre-waiting list LT treatment protocol consisting of localized concurrent chemoradiotherapy, followed by hepatic arterial infusion chemotheraphy. If patients had a good response, they were transplanted.

In Western countries, the San Camillo experience of downstaging strategy with trans-arterial radio-embolization achieved promising results for HCC with PVVT (19). The trans-arterial radio-embolization allows to downstage HCC and transplant patients with curative intents in the setting of LT (20,21).

External radiation therapy is an innovative choice for HCC. Therefore, as the HCC treatment paradigm continues to progress, ablative radiation therapy has moved onwards from a palliative treatment to both a bridge to LT and in some particular case to a definitive cure (22).

**Conclusions**

Many criteria have been published attempting to push the window open further than MC, and many demonstrate good and statistically similar results to MC. Expansion of MC recruits more LT candidates with HCC who cannot be treated by loco-regional therapy. To date though, none of them have found widespread acceptance in National allocation policies. Carefully selected patients beyond the traditional criteria for transplantation may achieve excellent LT outcomes through a planned, multidisciplinary approach to treatment.

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**Footnote**

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

**References**


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