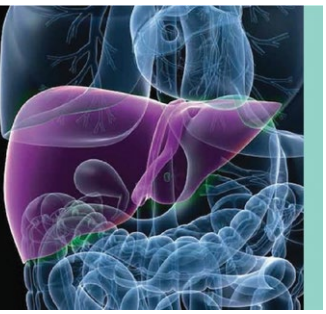

Looking for the Best Model to Predict Hepatocellular Carcinoma Recurrence After Liver Transplantation in Latin America

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The Milan criteria were published 20 years ago and have been established as standard selection criteria for liver transplantation (LT) in patients with hepatocellular carcinoma (HCC).[1] Currently, more than 2500 liver transplants per year are performed in Latin America, in which heterogeneous data have been reported regarding LT for HCC (Fig. 1). In most Latin American countries, the Milan criteria are most frequently used to select patients with HCC.

HCC recurrence after transplantation is a worrisome issue, considered a systemic advanced disease with poor survival rates and few therapeutic treatment resources. Although Milan criteria began a revolution regarding LT worldwide with excellent survival and low recurrence rates, predicting HCC recurrence purely and exclusively according to number and tumor size is currently under debate. A number of other predictive models have challenged candidate selection and categorization processes with a trend toward "hyperselection criteria" created to balance and ensure equitable access to organ allocation policies.[2-5] (Fig. 2)

The French alpha-fetoprotein (AFP) model, which includes serum AFP values, has been validated in external cohorts, including Latin America.[3,4] Serum AFP, both as a continuous variable and a dichotomous variable, has been associated with HCC recurrence independently from size and number and correlates with tumor dedifferentiation and microvascular invasion.[3-5] In addition, there is a renewed and increasing interest in AFP not only as a prognostic but also as a surveillance tool for HCC. Although the

Abbreviations: AFP, alpha-fetoprotein; CT, computed tomography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; LT, liver transplantation; mRECIST, modified RECIST; MRI, magnetic resonance imaging; NA, not assessed; OH, alcoholic liver disease; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; RETREAT, Risk Estimation of Tumor Recurrence After Transplant; SV, survival; UCSF, University of California, San Francisco; WL, waiting list.

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Potential conflict of interest: Nothing to report.

Received August 13, 2018; accepted October 9, 2018.

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Author	Country	Patients	Design	Etiology	Results
Gabrielli M Transplant Proc 2010	**CHILE**	29 HCC within/beyond Milan	**C Alemana** 1993-2009 Retrospective	HCV 44% OH 31%	**5-year OS >80% Milan out 66% Recurrence 13%**
Hoyos S Ann Hepatol 2015	**COLOMBIA**	54 HCC within/beyond Milan	**Medellín** 2004-2013 Retrospective	OH 22% HBV 20% HCV 18%	**5-year OS 74% Recurrence 7.4%**
Costa P. Transplant Proc 2010	**BRAZIL**	140 HCC within/beyond Milan	**Ceará** 2006-2010 Retrospective	HCV 45.7% OH 17.1% HBV 12.8%	**Recurrence 8.6%**
Felga G Transplant Proc 2012	**BRAZIL**	130 HCC within/beyond Milan	**S Paulo** 2004-2013 Prospective	NA	**Downstaging n = 10**
Ataide EC Transplant Proc 2011	**BRAZIL**	83 HCC within/beyond Milan	**Campinas** 1997-2010 Retrospective	NA	**Recurrence 6.0%**
Teixeira AC Transplant Proc 2010	**BRAZIL**	25 HCC within/beyond Milan	**S Paulo** 2001-2009 Retrospective	HCV 40% OH 29% HVB 7%	**Recurrence 12%**
Salvalaggio PR Am J Transplant 2015	**BRAZIL**	283 HCC within/beyond Milan	**S Paulo** 2001-2009 Retrospective	HCV 69% OH 12% HBV 7%	**Dropout 3 months, 6 months, 12 months: 6%, 12%, 18% SV post TH >3 m WL HR 0.28**
Gruz F Acta Gastro Lat 2013	**ARGENTINA**	95 HCC within/beyond Milan	**Bs As** 2006-2013 Retrospective	HBV 34% HCV 33% Crypto 29%	**5-year OS 67% Recurrence 19%**
Piñero F Ann Hepatol 2013	**ARGENTINA**	54 HCC within/beyond Milan	**Bs As** 2005-2010 Retrospective	HCV 46% HVB 16%	**5-year OS 68% Recurrence 15% Score**
Piñero F Eur J Gastroenterol Hepatol 2015	**ARGENTINA**	134 HCC within/beyond Milan/incidental	**Multicenter** 2005-2011 Retrospective	HCV 41% OH 19% HVB 12%	**Recurrence 13.7% Screening waiting list S 33% E 99%**

FIG 1 Cohort studies reporting survival or recurrence after LT for HCC in Latin America.

Achilles' heel lies in the different cutoffs considered, serum AFP greater than 1000 ng/mL has been considered a negative selection criteria for transplantation even in patients within Milan criteria.

Other authors proposed assessing pretransplant tumor dedifferentiation independently from imaging tumor burden.[6] However, tumor biopsy is sometimes not technically feasible. Moreover, the absence of microvascular invasion on the specimen does not completely exclude its presence (false-negative result), and regarding tumor differentiation, pathologists' interobserver agreements have challenged this algorithm.

Consequently, these slightly static variables do not take into account dynamic changes arising during time on the waiting list. In fact, some authors have underlined that in this period, a unique opportunity for a "natural" selection process between progressors and nonprogressors could be settled.[7] (Fig. 3) Time on the waiting list has been considered a key tool for tumor biology observation.[7] However, this proposal has many caveats, including possibility of treatment before transplantation, number and diameter of tumor nodules, serum AFP values, and regional differences related to donor scarcity and organ allocation policies. A crucial finding is that, regarding clinical decision-making processes, locoregional treatments are usually performed mainly considering imaging data rather than both imaging and AFP values. This biological marker should be taken into consideration when deciding whether to treat patients during the wait-list period (Fig. 3).

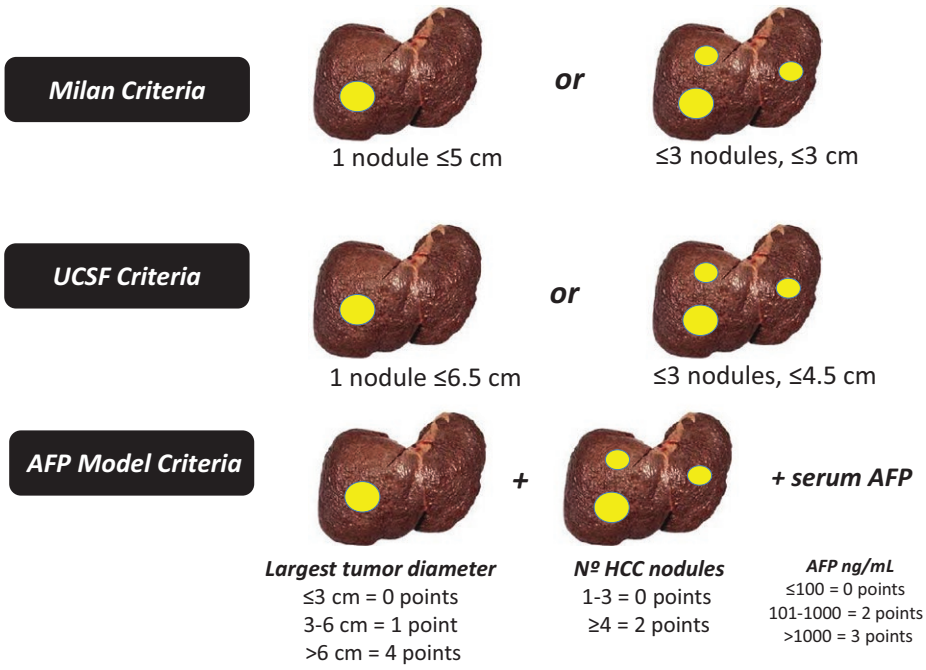

FIG 2 Transplant selection models.

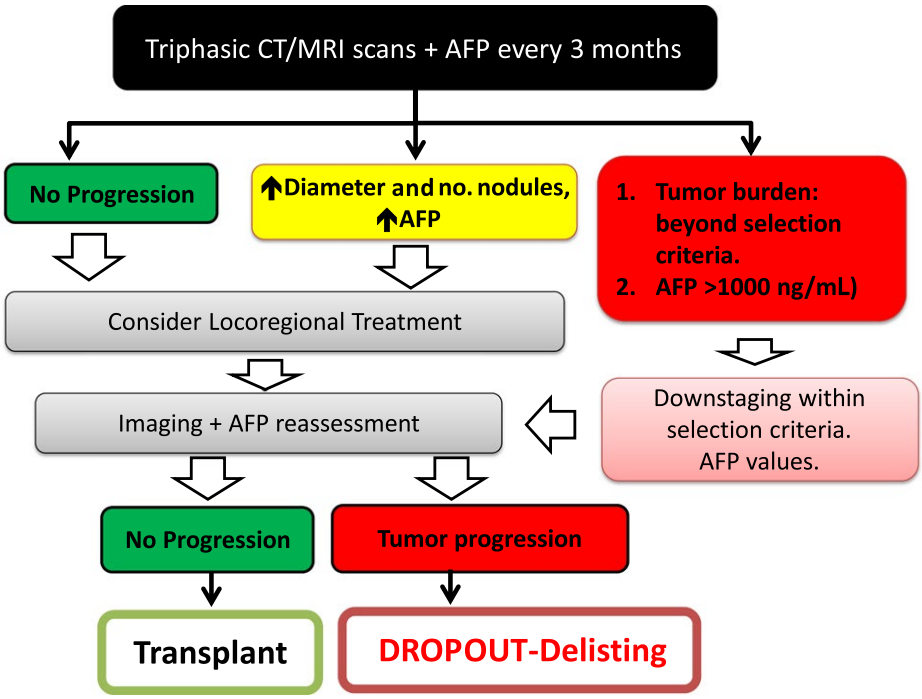

FIG 3 The multistep process of dynamic evaluation while on the waiting list for patients listed for LT and HCC.

In contrast, some patients beyond Milan criteria may have enough survival and low recurrence rates after downstaging with locoregional therapies.[8] However, evidence-based medicine using this approach still demands prospective and validation cohort studies. Moreover, definition of tumor response or progression after locoregional therapies during the waiting-list period demands further consensus processes (Fig. 3). Definition of tumor response

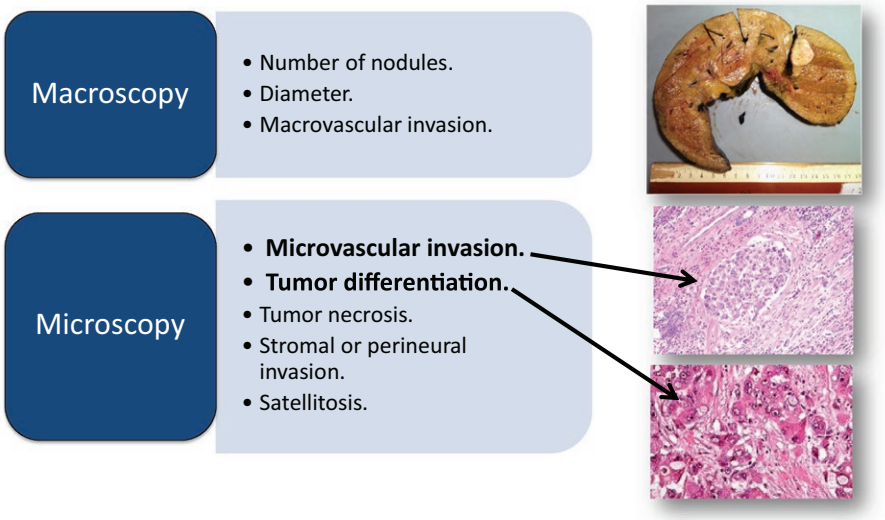

FIG 4 Explanted liver analysis and risk assessment.

or progression after locoregional treatments might be different when considering Response Evaluation Criteria in Solid Tumors (RECIST), modified RECIST (mRECIST), or just the aforementioned selection criteria for LT.[9] In fact, it may happen that radiological progression is considered according to mRECIST or RECIST and yet even that same patient is still within eligibility criteria for transplantation.

Consequently, the pretransplant candidate selection process should consider dynamic and longitudinal data instead of a static photograph of a single pretransplantation moment. These pretransplant predictive models provide a closed solution but still are not perfect. This is reflected by discordance observed between pretransplant images and explanted liver findings, which in some reports were greater than 30%.[3,4,6]

Finally, it is important to highlight the following issues when assessing the risk for HCC recurrence after LT. First, imaging-explanted liver discordance might be either a consequence of tumor progression on the waiting list ("false" discordance) or a "real" discordance in terms of low pretransplant imaging accuracy. Second, at which time point was this evaluation considered? For instance, an information bias can be caused by imaging assessment at time of inclusion on the waiting list when compared at last pretransplant imaging evaluation (information bias), thus not considering the effect of locoregional therapies performed (tumor necrosis in the explanted liver).

In spite of an adequate selection of candidates, recurrence risk reassessment with explanted liver data should be a priority focusing on the presence of microvascular invasion and tumor dedifferentiation (Fig. 4). The Up-to-7 criteria showed that the occurrence of microvascular invasion at any size or tumor number correlated with a significantly lower survival and higher recurrence rates. More recently, some predictive models have included pretransplantation and posttransplantation variables. The Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score[10] and the updated version of the Metroticket calculator[11] included tumor burden and AFP values.

In conclusion, there is a need for improvement in the selection process for HCC candidates for LT, aiming to expand the population and improve the selection process, taking into account a more equitable distribution of organs.

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