Editorial

Expanding the boundaries of Milan

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Comment on: Lee JH, Cho Y, Kim HY, *et al.* Serum Tumor Markers Provide Refined Prognostication in Selecting Liver Transplantation Candidate for Hepatocellular Carcinoma Patients Beyond the Milan Criteria. Ann Surg 2016;263:842-50.

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Since the publication by Mazzaferro in 1996, many centers in the US and Europe have been performing liver transplantation (LT) in selected hepatocellular carcinoma (HCC) patients with excellent outcomes. The article by Lee *et al.* (1), recently published in *Annals of Surgery* from a multi-centre study in Korea, brings up again the debate of whether expanding Milan criteria (MC) for LT could benefit selected patients. The authors proposed a novel score to predict recurrence and survival in HCC patients after LT. The MoRAL score is based on the power of alpha fetoprotein and prothrombin-induced by vitamin K absence-II (PIVKA-II), also called Des-γ-carboxyprothrombin (DCP), in predicting HCC recurrence (1).

Patients undergoing LT for HCC within MC have survival rates of 70% or better and recurrence rates around 15% (2). These results that have been validated in multiple studies around the world (3,4). The most important previously published risk factors for recurrence include vascular invasion, poor differentiation, tumor size >5 cm, and tumor stage outside MC (5). Efforts to expand the current selection criteria have so far been associated with a substantial decrease in survival. Notably, there is still great interest to find better ways to allocate organs in patients with HCC other than just by using tumor size and number of lesions. Currently, down staging HCC with transarterial chemoembolization (TACE) or thermal ablation remains a valid therapeutic option to make patients eligible for transplantation with comparable outcomes (6).

A low MoRAL score (cutoff of 314.8) was associated with significantly longer recurrence-free survival and overall survival, including those beyond and within the MC, which highlights the need of a more sophisticated selection system for LT in patients with HCC.

However, is this score applicable to patients in the Western world? As the authors stated in this report (1), their patient population has a very high incidence of hepatitis B infection and a predominant usage of living donor LT (LDLT). The population in the US and Europe transplanted with HCC has a much higher proportion of hepatitis C, alcoholic liver disease, and NASH patients with lower rates of hepatitis B virus infection (6). These differences in patient characteristics could result in differences in serum tumor marker expression and tumor biology (7,8). It is important to note that their reported overall recurrence rate of 30% is higher than the usual 15% reported in series from the Western world, which points toward some variances that could be attributed to differences in tumor characteristics, pre-transplant HCC management, LDLT, and waiting time.

In the US, deceased donor LT (DDLT) is commonly used. Due to the scarcity of organ availability for transplantation, strict criteria have been used to limit transplantation to patients with HCC who are likely to have good outcomes. Many argue that the MC is too restrictive and could potentially prevent some patients with favorable tumor biology to undergo LT (9). Many centers have used expanded criteria systems such as UCSF, Asian Medical Center, and the Toronto criteria to select patients for

LT (9,10).

One of the most interesting findings of this report was that patients within MC with high MoRAL score have significantly higher risk of recurrence than those beyond MC with low MoRAL score. Those with lower MoRAL scores had significantly longer survival (HR 2.59), which also correlated well with explant histology. PIVKA-II is considered to have a higher diagnostic accuracy, and its combination with AFP can improve the diagnostic sensitivity. Ito *et al.*, from Kyoto University, also incorporated PIVKA-II and defined their own criteria obtaining survival rates greater than 80% (11). Although the MoRAL score seems to predict recurrence very well, the use of serum markers such as AFP may be unreliable in around 30% of patients (12).

Tumor recurrence is not only related to tumor size and macroscopic radiologic appearance. Several serum and tissue biomarkers have been used to predict tumor behavior (13). Recent efforts have examined genetic mutations and protein expression of TP53, RET, glypican-3, TERT, β-catenin, and the presence of progenitor cells markers CD133, CD44, CD90, EpCAM, and others in HCC prognosis (13,14). Interesting recent data suggest that the microenvironment plays a major role in cancer prognosis. In HCC, the T cell to Treg ratio and the total number of infiltrating Tregs have been associated with poor outcomes. Likewise, the presence of tumor expression of PDL1 and PDL2 (ligands of PD1) have been correlated with inactivation of T cells during trafficking promoting a suppressive niche that can alter tumor progression and aggressiveness (14).

Prediction models should evolve to reflect changing patterns of risk, changing patterns of treatment, and new biologic understanding of tumorigenesis, microenvironment, and prognosis stratification. This study reflects a great deal of work by the authors to develop a novel but also user friendly selection system for HCC patients. A few questions remain. Are tumor biopsies necessary to evaluate tissue biomarkers and the infiltrate to assess prognosis prior to LT? Should we use serum biomarkers or a combination of serum and tissue biomarkers? Should this and other measures be part of a more sophisticated method of future personalized medicine to identify "good candidates" in HCC patients? Further studies are warranted to better define improved prognostic features to facilitate a broader patient selection of cancer patients that can potentially benefit from LT. It may be time to carefully revise the Milan criteria.

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Footnote

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

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