Editorial

It is time to abandon the Milan criteria

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Comment on: Halazun KJ, Tabrizian P, Najjar M, *et al.* Is it Time to Abandon the Milan Criteria?: Results of a Bicoastal US Collaboration to Redefine Hepatocellular Carcinoma Liver Transplantation Selection Policies. Ann Surg 2018;268:690-9.

Submitted Oct 15, 2018. Accepted for publication Oct 26, 2018.
doi: 10.21037/hbsn.2018.10.08
View this article at: http://dx.doi.org/10.21037/hbsn.2018.10.08

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm worldwide and the third most common cause of cancer-related death. Liver transplantation (LT), which offers the theoretical advantage of removing both the tumor and the organ that are at risk of developing future malignancy, is an established therapy for HCC in patients with liver cirrhosis. A shortage of cadaveric organs for transplantation continues to impair our ability to provide LT despite progress in surgical techniques and immunosuppression. Therefore, it is important to allocate the deceased donor livers with excellent results, and to ensure reasonable outcome for living donors who need to undergo invasive surgery.

The Milan criteria (MC) have significantly improved the outcome of LT for HCC and have become the gold standard to achieve a favorable outcome (1). Transplantation for patients within the MC generally reaches a 5-year overall survival rate of 70–80% and a recurrence rate of around 10%. Many groups have proposed LT for patients with large and numerous tumors because the favorable outcomes have raised the question of whether the selection criteria might be expanded (2,3). Another criticism against the MC is the lack of tumor biological indices to help dictate best oncological practice when transplanting HCC patients. Therefore, several centers have developed criteria that include tumor biological indices to predict outcome.

Organ shortages have forced patients with HCC to endure long waiting periods that are associated with tumor development. Currently, there is no consensus about how to manage patients with HCC while awaiting LT. Guidelines published in the UK state that locoregional therapy, such as transarterial chemoembolization, radiofrequency ablation, ethanol injection and microwave coagulation, should be considered for all listed patients with HCC (4). Although tumor markers would be changed by such locoregional therapy, current criteria fail to take into account the kinetics of tumor markers and the response to therapy (5,6).

The article by Halazun *et al.* recently published in *Annals of Surgery* attempted to resolve this problem (7). Halazun *et al.* used radiological criteria and α-fetoprotein (AFP) as a serum marker. They considered dynamic changes in AFP that would reflect treatment response after locoregional therapy, or as a surrogate of biological behavior for patients without treatment on the waiting list. AFP is recognized as a biological predictor of prognosis in HCC and has been included in many criteria. Halazun *et al.* pointed out that many criteria use AFP at a single time point, even though patients usually wait a long time until LT and undergo locoregional therapy for HCC during the waiting. Therefore, Halazun *et al.* have hypothesized that the dynamic changes in AFP served as a better predictor of recurrence and survival. They used AFP levels at diagnosis, maximum AFP at any time point, and the final immediate pretransplant AFP level. Cutoff levels of AFP were set at <200, >200 to 1,000, and >1,000. AFP <200 at any time point showed the best 5-year recurrence-free survival. Patients with maximum AFP >1,000 that fell to <1,000 before LT with a response that exceeded 50% had similar recurrence-free survival compared to patients with a maximum AFP of 200–1,000 that fell to <200 before LT. Halazun *et al.* suggested that using an initial AFP of >1,000 as an absolute contraindication to LT by other criteria may

result in the exclusion of a subset of patients that would benefit from LT and potentially be cured. Furthermore, they created a simple scoring system with three independent predictors of recurrence-free survival: maximum tumor size at diagnosis, maximum tumor number at diagnosis, and AFP response from maximum to final AFP level. The patients were divided into three groups according to the score, and there were significant differences in the cumulative incidence of recurrence between the groups. Furthermore, the score correlated with overall survival.

Tumor size and tumor number at diagnosis were included in the criteria despite the median waiting time from listing to LT exceeding 8 months, and >80% of patients received locoregional therapy while waiting. Although it might be hard to obtain the radiological data just before LT, the precise radiological data after locoregional therapy; tumor size and tumor number could predict the recurrence more accurately. Additionally, Halazun *et al.* demonstrated that the score correlated well with explant pathological tumor differentiation and vascular invasion. However, they did not report the extent of macrovascular and microvascular invasion.

Japanese groups have measured the impact of des-γ-carboxy prothrombin (DCP) levels on the outcome of living donor LT (LDLT) for otherwise unresectable and/or untreatable HCC patients (6,8). DCP level is well established as a sensitive and specific tumor marker in patients with HCC, and is an independent predictive factor of microvascular invasion. We previously reported that DCP level was significantly correlated with macroscopic invasion and intrahepatic metastasis in the explanted liver (6). The problem was that DCP was used at a single time point (immediately before transplantation) because all patients underwent scheduled LDLT without a long waiting time. More than half the patients received pretransplant locoregional therapy; therefore, dynamic changes in DCP from the initial treatment to pretransplant might be a better predictor of the outcome of LDLT, as in the study of Halazun *et al.*

Neutrophil-to-lymphocyte ratio (NLR) has emerged as a useful prognostic factor for the recurrence of several malignancies. An elevated NLR significantly increased the risk of HCC recurrence after LT (9) or LDLT (10). Halazun *et al.* did not incorporate any inflammatory markers in their study published in *Annals of Surgery*, although NLR was one of the independent predictors of recurrence by multivariate analysis. The authors felt that the understanding of how NLR was affected by locoregional therapy, increasing Model of End-Stage Liver Disease (MELD) score, or other recipient factors unrelated to HCC factors was poor. Elevated NLR correlates with microvascular invasion and poorly differentiated tumors. There are several possible explanations for the predictive role of preoperative elevated NLR (11). Infiltration of proinflammatory macrophages, cytokines, and chemokines in the tumor microenvironment can boost tumor growth, invasion, and metastases (12). Furthermore, high expression of granulocyte colony-stimulating factor in tumor tissue and macrophage colony-stimulating factor in peritumoral tissue is associated with elevated circulating neutrophils and poor prognosis (13). Another study showed that interleukin (IL)-17-producing T cells are thought to release chemokines that recruit neutrophils, leading to elevated NLR, and promote differentiation of tissue macrophages in peritumoral regions into tumor-associated macrophages (TAMs). Both IL-17-producing T cells and TAMs may accelerate tumor progression and antitumor T-cell exhaustion (10). The interpretation of NLR in patients with end-stage liver disease, often complicated with hypersplenism and pancytopenia, seems to need caution. Moreover, the kinetics of NLR should take into account the criteria.

Recently, the impact of lymphocyte-to-monocyte ratio (LMR) in LDLT for patients with HCC was reported (14). Low LMR was significantly associated with high AFP, high DCP, high NLR, larger tumor size, more tumors, and poorer prognosis. Low LMR was an independent prognostic factors, particularly among patients beyond the MC. LMR reflected the immune status of the tumor microenvironment in the explanted liver (14).

A Korean group reported that ^{18}F-FDG positron emission tomography (PET) positivity and AFP level were significant pretransplant prognostic factors by multivariate analysis, whereas tumor size and tumor number were not significant value for tumor recurrence or overall survival after LDLT (15). High standardized uptake value (SUV) by PET usually reflects poorly differentiated HCC, combined HCC, or HCC with sarcomatous change. The high cost of PET is problematic, thus, it is not performed universally or several times. Therefore, the kinetic changes in SUV would be hard to obtain.

In conclusion, Halazun *et al.* gives us an important concept that the dynamic changes in tumor markers should be checked and initial high levels of tumor markers are not a contraindication for LT. For such patients, we should offer locoregional therapy to reduce the tumor burden as far as liver function is allowed, and check the treatment response

before abandoning the LT.

Acknowledgements

Funding: This work was partly supported by JSPS KAKEN Grant Number (15H0579 and 18K08542), and by the Program for Basic and Clinical Research on Hepatitis from Japan Agency for Medical Research and Development.

Footnote

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

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Cite this article as: Yoshizumi T, Shirabe K, Mori M. It is time to abandon the Milan criteria. HepatoBiliary Surg Nutr 2019;8(1):56-58. doi: 10.21037/hbsn.2018.10.08

