Editorial

# Twenty years of Milan criteria: the wicked flee though no one pursues

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After the initial very disappointing results observed in the management of hepatocellular cancer (HCC) using liver transplantation (LT) (1), a revolution has started with the introduction of the Milan criteria (MC) (2). The very seminal paper from Mazzaferro has represented a real breakpoint respect to the past, consenting to obtain substantially similar survivals among tumoral and non-tumoral patients. However, despite the MC are connected with excellent patient survivals and low recurrence rates, only a very small percentage of HCC patients meet these so stringent criteria, with a small but not negligible percentage of MC-IN patients eventually experiencing a post-LT recurrence. As a consequence, several expanded criteria have been proposed with the intent to enlarge the population of potentially transplantable patients and to further reduce the risk for HCC recurrence: however, only the San Francisco criteria proposed by Yao (3) and the Up-to-seven Criteria proposed by Mazzaferro (4) have obtained a worldwide clinical validation. Thus, despite twenty years have passed away from their introduction, the MC still remain the cornerstone of HCC selection for LT. The reason for the enduring success of the MC is connected with the fact that (I) they are easy to use; and that (II) they perfectly fall into a sort of "grey area" in which patient survivals are excellent also when radiology underestimates the cancer. As shown by Decaens (5), MC still excellently work also when the explanted liver is taken into account, but if we step-up to the (slightly) enlarged San Francisco Criteria, survivals fall and recurrences increase. However, we know that morphology alone do not tell us the entire story. Recent publications aimed at identify new selection tools able to detect "high-risk-for-recurrence" HCC patients have focused their attention on alpha-fetoprotein modification, radiological response after loco-regional treatments and inflammatory markers (6-10). We know MC still continue doing a great job in selecting patients with high risk for recurrence. However, some of these "wicked" tumors still continue fleeing. New criteria integrating HCC morphology and biology are strongly needed with the intent to "capture" all of them.

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## Footnote

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

## References

1. Iwatsuki S, Klintmalm GB, Starzl TE. Total hepatectomy and liver replacement (orthotopic liver transplantation) for primary hepatic malignancy. World J Surg 1982;6:81-5.
2. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-9.
3. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology

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2001;33:1394-403.
4. Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35-43.
5. Decaens T, Roudot-Thoraval F, Hadni-Bresson S, et al. Impact of UCSF criteria according to pre- and post-OLT tumor features: analysis of 479 patients listed for HCC with a short waiting time. Liver Transpl 2006;12:1761-9.
6. Duvoux C, Roudot-Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143:986-94.e3; quiz e14-5.
7. Lai Q, Levi Sandri GB, Lerut J. Selection tool alpha-fetoprotein for patients waiting for liver transplantation: How to easily manage a fractal algorithm. World J Hepatol 2015;7:1899-904.
8. Otto G, Schuchmann M, Hoppe-Lotichius M, et al. How to decide about liver transplantation in patients with hepatocellular carcinoma: size and number of lesions or response to TACE? J Hepatol 2013;59:279-84.
9. Lai Q, Avolio AW, Graziadei I, et al. Alpha-fetoprotein and modified response evaluation criteria in solid tumors progression after locoregional therapy as predictors of hepatocellular cancer recurrence and death after transplantation. Liver Transpl 2013;19:1108-18.
10. Lai Q, Castro Santa E, Rico Juri JM, et al. Neutrophil and platelet-to-lymphocyte ratio as new predictors of dropout and recurrence after liver transplantation for hepatocellular cancer. Transpl Int 2014;27:32-41.

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