Editorial on Milan Criteria

Historical perspective on the importance of the Milan criteria

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Twenty years ago, the most important article regarding hepatocellular carcinoma and liver transplantation was published. Mazzaferro's article in the *New England Journal of Medicine* did not try to overstate its importance. The paper's conclusion: "Liver transplantation is an effective treatment for small, unresectable hepatocellular carcinomas in patients with cirrhosis" seemed reasonable and not considered unusually revolutionary (1). Hepatocellular carcinoma (HCC) had been an indication for liver transplantation from the earliest days and reports. Three of the first six patients described by Starzl in his landmark 1963 article and follow up article in 1965 had hepatocellular carcinoma (2,3). Many liver transplant programs in the United States started with a large percentage of HCC patients as these patients were technically easier than the patients with severely decompensated end stage liver disease. However the excitement of short term survival gave way to the realization that long term survival in many of these HCC patients undergoing liver transplantation was still elusive and questioned the utility of transplanting patients with HCC (4). Further complicating the issue of transplantation for HCC was the fact the Medicare (the Federal funding source for health care of the elderly and disabled) would not pay for liver transplantation for hepatocellular carcinoma. The time period between 1990 and 1996 and the publication of the Mazzaferro paper witnessed publications from every major liver transplant center in the world describing their experience with adjectives ranging from controversial to poor (5 year survival roughly approximately 30%) (4-15). As more centers reported discouraging results additional modalities such as chemotherapy was added either before or after transplantation to decrease the risk of recurrence (5). Multi center trials were discussed to determine the role of liver transplantation ± chemotherapy but could not get funded.

Thus, the status of liver transplantation as an effective treatment modality for HCC in 1996 was highly questionable. While the optimists noted that 30% of the patients are alive at 5 years whereas they all would have died within 2 years without transplantation, the increasing shortage of liver grafts started making utility a stronger argument in terms of allocation policy. It would be hard to argue that a patient with primary biliary cirrhosis and a >80% probability of survival at 5 years is a better use of an organ than someone who has a 30% chance of survival. Mazzaferro's article had just 48 patients which was far smaller than many of the other published reports of liver transplantation for the treatment of HCC at the time. What made the Mazzaferro's experience different and successful was adhering to strict selection criteria for transplantation. Those criteria which have become known worldwide as the "Milan criteria" are a solitary tumor $\leq$5 cm, or no more than three lesion each less than 3 cm (1). Strict adherence to these criteria led to a survival roughly equivalent to non-tumor patients undergoing liver transplantation, thus these patients had equal organ utilization and could be included in allocation algorithms. This demonstration of equivalent survival with non HCC patients allowed Medicare in 2001 to justify paying for transplants for selected (Milan criteria) patients with HCC.

Twenty years have now elapsed since the Mazzaferro publication and wide acceptance of the Milan criteria in the United States and worldwide. There have been many other criteria published attempting to push the window open further than Milan's criteria and many demonstrate good and statistically similar results to Milan such as

Hangzhou, UCSF, ASAN, Toronto, and Tokyo among others, but none of them have found widespread acceptance in National allocation policies (16-20). The lack of diversity in allocation policy is a potentially problematic area. Diversity assists evolution of new ideas and methods of treatment. Furthermore, the continuous outside evaluation of results and need to keep results excellent places a barrier in trials to determine which other patients with HCC may benefit from liver transplantation. It is possible that with the external forces now placed on transplant programs, a trial such as was published by Mazzaferro might not be able to be completed today and thus the effective treatment of selected patients with HCC with liver transplantation might not have evolved such that 22% of the liver transplants performed in the US in 2016 were performed for patients within the Milan criteria. While we must adhere to National allocation system, we must also encourage clinical trials that push the boundaries of patient selection to ensure that liver transplantation can benefit the maximum number of patients.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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