Editorial

Liver transplantation for hepatocellular carcinoma: pushing the boundaries

Joanne M. O'Rourke, Shishir Shetty, Tahir Shah, M. Thamara P. R. Perera

Liver Unit, Queen Elizabeth Hospital, Birmingham, UK

Correspondence to: M. Thamara P. R. Perera, FRCS. The Liver Unit, Queen Elizabeth Hospital, Birmingham, UK. Email: Thamara.Perera@uhb.nhs.uk.

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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.

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Liver transplantation for hepatocellular carcinoma (HCC) has come a long way since the early days of high recurrence rates and the questions over whether liver transplantation should really be used for treating malignancy (1,2). Transplantation is now firmly established as a curative option for a select group of patients with HCC. Unfortunately, we still deny many patients with this cancer the option of transplantation because of adherence to old patient selection criteria that excludes many on grounds of inadequate survival benefit when comparing to non-HCC indications for liver transplantation.

The early concerns of unacceptably high recurrence rates were overcome by the landmark study by Mazzaferro *et al.*, published in 1996, which provided criteria based on tumor size and number that achieved excellent long-term recurrence-free survival (RFS) (3). This has repeatedly been validated. These criteria referred to as the Milan Criteria (MC) achieved over 70% 5-year survival when adhered to and were therefore globally adopted (4,5). However, this score was based on analysis of the best available data at that time. There has since been a great deal more experience and knowledge gained in this field of practice. This has led to a better understanding of the role of biology as well as tumor bulk in RFS after transplantation. These insights are leading to refinement of criteria for liver transplantation to allow expansion of application of transplantation without compromising outcomes. The University of California, San Francisco (UCSF) criteria have demonstrated that criteria based on pre-operative imaging can be expanded with outcomes comparable to the MC (6-8).

Anyone involved with the follow-up care of patients who are transplanted for HCC will know that there are patients with small tumors within the MC who develop recurrence and patients with larger tumors on the limit of, or beyond, accepted radiological criteria who are cured by transplantation. It is therefore widely accepted that we need to better understand the complex tumor biology of HCC and to incorporate available markers for this into our algorithms. The most widely incorporated biological marker is α-fetoprotein (AFP). An AFP >1,000 ng/mL is associated with reduced survival (7). Duvoux *et al.* proposed a model in 2012 that incorporated AFP and demonstrated AFP predicted tumor recurrence. The model included tumor size, number of tumors and AFP, and a score greater than 2 was predictive of increased 5-year recurrence 50.6% *vs.* 8.8% for a score of 2 or less (9). AFP now widely features in the listing criteria for many liver transplant centers but not all, and in those that employ AFP there is variability in cut-offs (9-12).

It is also important to note the use of loco-regional therapy as a bridge to transplant is becoming standard practice. Additionally, downstaging is increasingly accepted for patients who would otherwise be ineligible for liver transplant based on the size and number of tumors and in some cases AFP. This adds another level of complexity to the field and how we incorporate AFP in this cohort of patients. Both the European Association for the Study of Liver Diseases (EASL) and the American Association for

the Study of Liver Diseases (AASLD) guidelines do not incorporate AFP cut-offs into their recommendations at this time based on grading of available evidence although many regional guidelines do.

Several centers utilise AFP when making decisions regarding listing for transplantation. AFP is dynamic and we see fluctuations from AFP secreting tumors depending on how long a patient remains on the waiting list and whether any locoregional therapy is administered. It has been previously shown that only the last pre-transplant AFP predicts survival and that downstaging AFP can be associated with good overall survival (13). One study showed that patients with AFP levels which had decreased to ≤400 ng/mL post locoregional therapy didn't differ significantly in their post-transplant survival rates compared to patients with an AFP persistently ≤400 ng/mL (89% *vs.* 78% at 3 years, P=0.11) (13).

Halazun *et al.* in October of this year published in *Annals of Surgery* a novel approach to how we utilise and interpret AFP dynamics (14). This study was constructed using three prospectively maintained databases from the following transplant centers: New York Presbyterian Hospital Center for Liver Disease and Transplantation (Columbia University Medical Center and Weill Cornell Medicine), Mount Sinai School of Medicine, and UCLA. They examined data from liver transplants performed between 2001 and 2013. The authors define a new value referred to as AFP response (AFP-R) which measures differences between maximum and final pre-liver transplantation AFP in HCC patients. Eighty-four percent of the 1,450 patients reviewed had received locoregional therapy. The primary outcome which is of paramount importance when looking at cancer outcomes was appropriately 5-year RFS. Of 1,450 patients looked at just over 16% were outside MC. They went on to show that independent predictors of RFS included tumor size, number of tumors and AFP-R on both univariate and multivariate analysis. A cox regression analysis was performed to establish appropriate cut-offs and these independent predictors of poor RFS used to establish a new scoring system The New York/California (NYCA) score. The scoring system is based on the hazard ratios (HRs) of these independent predictors of 5-year RFS. The HRs from the cox regression model were rounded to the nearest whole number and patients assigned points. To calculate the final NYCA score, the scores for each variable, maximum tumor size at diagnosis, number of tumors and AFP-R, are added to generate a final score between 0–14. The simplicity of this scoring system adds to its potential utility in that it can be calculated using non-invasive parameters in the clinic setting, this is an important prerequisite for any proposed model which is intended for clinical application. The score is used to define categories for low, acceptable or high risk of recurrence with 5-year RFS of 90%, 70% or 42% respectively.

A competing risk regression analysis demonstrated a significant difference in cumulative incidence of recurrence between the three recurrence risk categories (P<0.0001) and they correlated with overall survival with significant differences seen between the groups. The authors then pleasingly went onto demonstrate the scoring system also correlated well to the known high-risk pathological features of tumor differentiation and vascular invasion.

AFP cut-offs for transplantation vary in different models and within centers that have adopted its usage. The French Duvoux score excludes listing for those with an AFP >1,000 ng/mL (9) and within the United Kingdom (UK) liver transplant program there is also a listing cut-off of 1,000 ng/mL. Toronto use a total tumor volume (TTV) of 115 cm^3 cut off along with an AFP cut-off value of 400 ng/mL (TTV/AFP model) (10). The authors in this recent study characterised patients using AFP levels ≤200, >200–1,000, >1,000 ng/mL and demonstrated differences in 5-year RFS between the groups with a P value <0.05 for all. Of particular note the cox regression analysis of AFP-R showed that the HRs for the group that had AFPs exceeding 1,000 ng/mL but that fell below 1,000 ng/mL before transplant, with a response that exceeded 50%, had RFS comparable to those who had a max AFP 200–1,000 ng/mL which fell to below <200 ng/mL before transplant with cumulative hazard of recurrence 24.5% and 24.1 % described. Unsurprisingly levels that fell below 200 ng/mL had the best 5-year outcomes.

This is not the first study to look at changes in AFP and outcomes for HCC (13,15-17), however, studies to date have predominantly been in the context of predicting survival post locoregional therapy or systemic chemotherapy, but there has been evidence supporting AFP velocity in predicting transplant outcomes published previously (18). The study by Halazun *et al.* is unique in that it not only looks at AFP-R in the context of HCC recurrence post liver transplantation but also goes onto incorporate it into a model for predicting RFS, alongside traditional markers of tumor size and number pre-transplant. In their discussion they highlight that some patients who would traditionally have been excluded for listing by the MC would fall into the low/acceptable risk categories with favourable 5-year

survival approaching 70%.

It is to be noted that with the proposed NYCA scoring system the radiological characteristics incorporated are from the time of diagnosis, this maybe different to the size and numbers of tumors on imaging at the time of transplant especially if the patient has severe hepatic decompensation and is deemed not suitable for locoregional therapy, the assumption would be that in prospective usage the scores are updated at intervals. In terms of radiological changes post locoregional therapy the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria is frequently employed (19) and it is not clear whether this could be used in the proposed scoring system. Radiological tumor response to loco-regional therapy is also a surrogate for tumor biology (20). Indeed, a good response to neo-adjuvant loco-regional therapy, as assessed by measuring remnant vital tissue, is associated with reduced tumor recurrence even in those within MC criteria (21). Further supporting the concept that response to loco-regional therapy provides valuable information about tumour biology and risk of recurrence post-transplant and highlighting the requirement to be able to non-invasively assess treatment response in order to model for risk of recurrence.

A key omission of this study is the time from diagnosis to transplant. The authors have acknowledged and addressed this in their discussions. The data however is convincing that AFP-R plays a role in the assessment of tumor biology prior to transplantation. A further validation study incorporating all patients listed and not just those who were actually transplanted would provide a more robust evaluation of AFP-R and the NYCA model. Despite this omission, it is most noteworthy that the cohort of patients who had an AFP >1,000 ng/mL but achieved an AFP reduction >50% had favourable outcomes which supports the argument that there are a cohort of patients who can be successfully down-staged from an unacceptably high AFP. The evidence for incorporating AFP into listing criteria globally has a strong case and is already widely utilised. The challenge is to incorporate imaging characteristics and the dynamics of AFP together. The model proposed does this and deserves further prospective validation. In answer to the question Halazun *et al.* posed "*Is it Time to Abandon the Milan Criteria?*", we could argue we already have moved on from the original MC in many liver transplant centers, although not all. Another important question worth asking is what is acceptable RFS for transplantation for HCC? To answer this, we must consider wait list drop out for non-HCC indications. In countries where there are national guidelines which determine the criteria for transplantation in HCC, it is important that we still have an opportunity to downstage patients outside criteria and doing this through a national downstaging evaluation enables the robust collection of prospective data with regular evaluation of outcomes against established models and novel models like NYCA. However, this is only the first step of proposing the best possible treatment; if we want to expand criteria, we must also ensure we have sufficient organ availability; which is presently a major limiting factor. Increasing organ availability is essential, so we ensure those within agreed criteria are transplanted in a timely manner and reduce wait list drop out. A reflection of the present situation in the UK is that we have seen an exponential increase in patients with HCC receiving organs from donation after circulatory death (DCD) donors instead of "preferred quality" organs from donation after brain death (DBD) donors.

The additional use of marginal organs and developing methods of assessing the viability of organs that would traditionally be discarded is certainly, in part, going to help address wait list drop out and give us the resources to push boundaries further in HCC transplantation. There is already tremendous effort going into exploring methods of viability testing of marginal livers to expand the donor pool (22). The overarching aim of the transplant community is to get closer to providing life prolonging liver transplantation to everyone who has the potential to benefit significantly.

HCC is now regularly described as an epidemic and worldwide is reported to be the second leading cause of cancer related deaths (23). In over 80% of patients, it occurs in the context of cirrhosis and despite advances in hepatitis B vaccination programs and the era of Direct Acting Antivirals for hepatitis C, the incidence of cirrhosis is increasing in part due to the increase in non-alcoholic fatty liver disease. From the release of the welcomed MC in an earlier era where clearly recurrence rates were unacceptably high, we then moved to a sense of unease that too much restriction may deny patients potentially curative liver transplantation. The intention is cure and with non-surgical treatment options the median increase in survival is frequently measured in months. The balance is to define algorithms that can predict recurrence, an outcome that is clearly devastating for the recipient and graft survival. Can we push boundaries? We have done so since 1996 and there will be patients who have benefitted from this. We should recognise the contribution of the MC to improving RFS and expand, as many centers across the world already have,

and AFP-R is a promising variable which warrants further attention and validation. Actively seeking new biomarkers for HCC which can enhance our ability to understand the biology of a tumor and making better use of existing biomarkers, like AFP, and the information they yield on rate of tumor progression, response to locoregional therapy and likelihood of recurrence is key. The work of Halazun *et al.* is timely and contributes to ongoing efforts to identify all those patients who will benefit from transplantation in the HCC cohort, they have identified new tools to explore in AFP-R and the NYCA score for risk stratification.

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Footnote

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

References

1. Olthoff KM, Millis JM, Rosove MH, et al. Is liver transplantation justified for the treatment of hepatic malignancies? Arch Surg 1990;125:1261-6; discussion 1266-8.
2. Ringe B, Pichlmayr R, Wittekind C, et al. Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. World J Surg 1991;15:270-85.
3. 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.
4. Jonas S, Bechstein WO, Steinmuller T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. Hepatology 2001;33:1080-6.
5. Mazzaferro V, Bhoori S, Sposito C, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. Liver Transpl 2011;17 Suppl 2:S44-57.
6. Yao FY, Hirose R, LaBerge JM, et al. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. Liver Transpl 2005;11:1505-14.
7. 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 2001;33:1394-403.
8. Duffy JP, Vardanian A, Benjamin E, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. Ann Surg 2007;246:502-9; discussion 509-11.
9. Duvoux C, Roudot-Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including alpha-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012;143:986-94.e3; quiz e14-5.
10. Toso C, Meeberg G, Hernandez-Alejandro R, et al. Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: A prospective validation. Hepatology 2015;62:158-65.
11. Hong G, Suh KS, Suh SW, et al. Alpha-fetoprotein and (18)F-FDG positron emission tomography predict tumor recurrence better than Milan criteria in living donor liver transplantation. J Hepatol 2016;64:852-9.
12. Yao FY, Mehta N, Flemming J, et al. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. Hepatology 2015;61:1968-77.
13. Merani S, Majno P, Kneteman NM, et al. The impact of waiting list alpha-fetoprotein changes on the outcome of liver transplant for hepatocellular carcinoma. J Hepatol 2011;55:814-9.
14. 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.
15. Rungsakulkij N, Suragul W, Mingphruedhi S, et al. Prognostic role of alpha-fetoprotein response after hepatocellular carcinoma resection. World J Clin Cases 2018;6:110-20.
16. Kao WY, Chiou YY, Hung HH, et al. Serum alpha-fetoprotein response can predict prognosis in hepatocellular carcinoma patients undergoing radiofrequency ablation therapy. Clin Radiol 2012;67:429-36.
17. Chou WC, Lee CL, Yang TS, et al. Changes in serum alpha-fetoprotein level predicts treatment response and survival in hepatocellular carcinoma patients and literature review. J Formos Med Assoc 2018;117:153-63.
18. Vibert E, Azoulay D, Hoti E, et al. Progression of alphafetoprotein before liver transplantation for hepatocellular carcinoma in cirrhotic patients: a critical

factor. Am J Transplant 2010;10:129-37.
19. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52-60.
20. Nicolini D, Agostini A, Montalti R, et al. Radiological response and inflammation scores predict tumour recurrence in patients treated with transarterial chemoembolization before liver transplantation. World J Gastroenterol 2017;23:3690-701.
21. Manzia TM, Lai Q, Iesari S, et al. Impact of remnant vital tissue after locoregional treatment and liver transplant in hepatocellular cancer patients, a multicentre cohort study. Transpl Int 2018. [Epub ahead of print].
22. Laing RW, Mergental H, Yap C, et al. Viability testing and transplantation of marginal livers (VITTAL) using normothermic machine perfusion: study protocol for an open-label, non-randomised, prospective, single-arm trial. BMJ Open 2017;7:e017733.
23. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.

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