Editorial on Milan Criteria

Hepatocellular carcinoma (HCC) recurrence and what to do when it happens

Adam S. Bodzin

Department of Surgery, Section of Abdominal Organ Transplantation, University of Chicago, California, USA

Correspondence to: Adam S. Bodzin, MD. Assistant Professor of Surgery, 5841 S. Maryland Ave., Room J517, MC5027, Chicago, IL 60637, USA. Email: abodzin@surgery.bsd.uchicago.edu.

Submitted Nov 15, 2016. Accepted for publication Nov 22, 2016.
doi: 10.21037/hbsn.2016.11.06
View this article at: http://dx.doi.org/10.21037/hbsn.2016.11.06

As we know, gold standard therapy for hepatocellular carcinoma (HCC) with underlying liver disease is orthotopic liver transplantation (OLT) given that the malignant burden is within certain criteria. Prior to 1996, outcomes were quite poor with 5-year survival reported as low as 20% (1) with transplants being performed without impedance for all tumors of all sizes. Thankfully, Mazzaferro *et al.* developed the Milan criteria changing the face of OLT for HCC for the next 20 years with improved overall survival at 5 years over 70% (2). While many groups have modified their criteria for transplantation of HCC patients with some including tumor markers and more lenient size criteria, the Milan Criteria still remains the standard by which HCC exception points are awarded in many areas of the world.

Biomarkers such as alpha feta protein (AFP), Protein Induced by Vitamin K Absence -II (PIVKA-II) or Des-gamma carboxyprothrombin (DCP), amongst others have been included in some areas of the world for assessment during OLT evaluation for HCC, as these may help add more tumor biology to simple size and number criteria (3,4). In the United States we continue to award exception points based on the Milan Criteria, yet there are proposals to begin to include biomarkers in the criteria for exception, which will add additional tumor biology to the decision making process (5). Unfortunately, despite improved predictive models, we still will encounter a considerable number of recurrences, as rates after transplantation range from 8-21% (6,7). One of the newer accurate models of recurrence was created by Agopian *et al.* who generate a predictive nomogram (c-statistic of 0.85) which includes numerous biomarkers that may help guide our management of HCC patients who undergo OLT (8). Unfortunately, some of the best indicators of post transplant recurrence are based on explant pathology, but this nomogram brings to light other potential indicators of tumor biology. The model demonstrates that neutrophil to lymphocyte ratio (NLR) is one of the more powerful predictors of tumor recurrence, a finding which has been shown in HCC as well as across numerous other malignancies. The nomogram takes NLR along with AFP and total cholesterol to broaden the assessment of tumor and recipient biology. These laboratory values are available at time of transplant and should be evaluated when considering borderline potential HCC candidates. Additionally, it takes into account known explant characteristics of vascular invasion and tumor grade which unfortunately limit the ability for this model to select for patients pretransplant.

First, the concept of what to do with recipients of OLT for HCC should be better defined. With numerous tools including AFP, AFP-L3%, DCP, NLR, and recurrence prediction models, we can assign risk to each patient (9). We must not ignore the information at our fingertips and need to remain attentive to tumor biology given explant pathology and tailor immunosuppression and surveillance for each individual patient. With the host of information we have we must adapt and provide personalized medicine within the realm of transplantation and malignancy.

What we know is that even with evolving tools and prediction capability, we will be saddled with tumor recurrence. Clearly when patients recur, prognosis is undoubtedly poor. The majority of patients usually present with multifocal recurrences making them difficult to treat, often affording patients little hope for long-term survival. One earlier study in 2004 reported that 32% of patients were able to undergo potentially curative resection and ultimately a 47% post-transplant survival (10). The data

is, however, limited about what happens to patients post-recurrence, but sadly this is a dilemma many patients and transplant providers must address. The question remains: what to do with them? How do we talk to patients and what options do we have for them? The literature is relatively scarce on what happens to patients post-recurrence. In one of the earlier papers examining post transplant recurrence, it was demonstrated that patients who suffered from acute rejection had worse long-term outcomes likely related to increase in immunosuppression. This finding should again make transplant physicians pause and evaluate each singular patient and lead to adjustments to minimize patient's immunosuppression. We must demonstrate caution when treating HCC patients for acute rejection and ultimately monitor them according to known increased risk.

A common theme in post-transplant recurrence is not surprisingly: the earlier recurrence, the worse outcomes with regards to mortality (11,12). Very early recurrence is likely a surrogate for systemic disease or extrahepatic disease at time of transplant or very aggressive tumor biology that may seed the host at time of transplant. Unfortunately these cases are unavoidable and options for these patients remain limited. In some circumstances, however, patients may present with resectable disease, which may be addressed. Long-term survival maybe possible with aggressive treatment with 5-year survivals reported over 50% in specific subsets of populations (13). This gives hope and opportunity to the transplant community to address identification of recurrence early and affording patients a chance at meaningful survival. Albeit surgery is clearly an excellent prognostic factor with regards to HCC recurrence, it biases most risk analysis. These patients are already destined for improved outcomes because resectability in most cases implies less tumor burden.

A recent comprehensive analysis was created examining mortality after tumor recurrence excluding intervention and therapies to limit underlying bias (14). Again, time to recurrence is one of the worst prognostic factors, but fascinatingly MELD score was the poorest predictor of mortality after recurrence. This can be explained by perhaps the long term weakened state of these patients at time of recurrence limiting options for therapy or perhaps their underlying prolonged overly immunosuppressed state while deconditioned allowing for more aggressive recurrences. Additionally, NLR was found to be an independent predictor of mortality in this model for mortality after recurrence; perhaps again a representative of the inflammatory milieu at time of transplant. This risk model includes a host of other factors allowing for a scoring system that can label recipients in different risk categories. The outcomes for aggressive intervention within lower risk groups certainly should provide hope to providers and patients that there is not a "one size fits all" outcome for patients with recurrence.

Moving forward we must continue to include markers for tumor biology when considering OLT candidates with HCC, but unfortunately we will remain burdened with tumor recurrences. We must, as a community, evaluate each OLT recipient with a personalized approach, as we may be able to afford them a chance for meaningful survival if they are to recur.

Acknowledgements

None.

Footnote

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

References

1. Ringe B, Wittekind C, Bechstein WO, et al. The role of liver transplantation in hepatobiliary malignancy. A retrospective analysis of 95 patients with particular regard to tumor stage and recurrence. Ann Surg 1989;209:88-98.
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. Takada Y, Uemoto S. Liver transplantation for hepatocellular carcinoma: the Kyoto experience. J Hepatobiliary Pancreat Sci 2010;17:527-32.
4. Zheng SS, Xu X, Wu J, et al. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. Transplantation 2008;85:1726-32.
5. Prentice M. Changes to HCC criteria for Auto Approval. Available online: https://optntransplanthrsagov/media/1922/liver_hcc_criteria_for_auto_approval_20160815pdf. 2016.
6. 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.

7. Sotiropoulos GC, Molmenti EP, Lösch C, et al. Meta-analysis of tumor recurrence after liver transplantation for hepatocellular carcinoma based on 1,198 cases. Eur J Med Res 2007;12:527-34.
8. Agopian VG, Harlander-Locke M, Zarrinpar A, et al. A novel prognostic nomogram accurately predicts hepatocellular carcinoma recurrence after liver transplantation: analysis of 865 consecutive liver transplant recipients. J Am Coll Surg 2015;220:416-27.
9. Chaiteerakij R, Zhang X, Addissie BD, et al. Combinations of biomarkers and Milan criteria for predicting hepatocellular carcinoma recurrence after liver transplantation. Liver Transpl 2015;21:599-606.
10. Roayaie S, Schwartz JD, Sung MW, et al. Recurrence of hepatocellular carcinoma after liver transplant: patterns and prognosis. Liver Transpl 2004;10:534-40.
11. Kornberg A, Küpper B, Tannapfel A, et al. Long-term survival after recurrent hepatocellular carcinoma in liver transplant patients: clinical patterns and outcome variables. Eur J Surg Oncol 2010;36:275-80.
12. Toso C, Cader S, Mentha-Dugerdil A, et al. Factors predicting survival after post-transplant hepatocellular carcinoma recurrence. J Hepatobiliary Pancreat Sci 2013;20:342-7.
13. Sapisochin G, Goldaracena N, Astete S, et al. Benefit of Treating Hepatocellular Carcinoma Recurrence after Liver Transplantation and Analysis of Prognostic Factors for Survival in a Large Euro-American Series. Ann Surg Oncol 2015;22:2286-94.
14. Bodzin AS, Lunsford KE, Markovic D, et al. Predicting Mortality in Patients Developing Recurrent Hepatocellular Carcinoma After Liver Transplantation: Impact of Treatment Modality and Recurrence Characteristics. Ann Surg 2016. [Epub ahead of print].

Cite this article as: Bodzin AS. Hepatocellular carcinoma (HCC) recurrence and what to do when it happens. HepatoBiliary Surg Nutr 2016;5(6):503-505. doi: 10.21037/hbsn.2016.11.06

