Letter to the Editor

Challenges in patient selection for liver resection or transplantation in patients with hepatocellular carcinoma beyond Milan criteria

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Provenance: This is an invited Letter to the Editor commissioned by Editor-in-Chief Yilei Mao (Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China).

Response to: Tanaka K. Resection versus transplantation for hepatocellular carcinoma exceeding Milan criteria within increasing donor shortage. HepatoBiliary Surg Nutr 2017;6:280-3.

Submitted Jun 26, 2017. Accepted for publication Jul 13, 2017.
doi: 10.21037/hbsn.2017.07.04
View this article at: http://dx.doi.org/10.21037/hbsn.2017.07.04

We are grateful to Dr. Tanaka (1) and Dr. Kays and his group (2) for their thoughtful comments and questions with respect to our study (3). We agree that patient selection is paramount and differences in patients with hepatocellular carcinoma (HCC) who are beyond Milan criteria and who are selected for either liver resection or transplantation are important to understand. Undoubtedly, there are patients in this category who are not candidates for transplantation. These patients usually have one or more of the following characteristics: advanced age, significant cardiovascular comorbidities, poor socioeconomic infrastructure, active mental illness, or characteristics of aggressive tumor biology. Importantly, there are also significant differences in regional, national, and continental resources directly affecting liver donor availability and use. Conversely, there are patients who are not candidates for resection due clinically significant cirrhosis (with either MELD or CPT beyond cut-off criteria), or clinically significant portal hypertension, or multifocal bi-lobar tumors, or technical limitations of operative techniques. And, of course, majority of patients with HCC beyond Milan criteria are not candidates for either resection or transplantation. To equate all these patients into one group is not possible. Patients with HCC benefit from multi-disciplinary collaboration to select best treatment for each patient.

The positive impact of tumor downstaging on survival was highlighted by both authors. Indeed, patients who were successfully downstaged prior to liver transplantation had the greatest overall and disease survival. Unfortunately, only 5% of patients in our study had neoadjuvant therapy prior to liver resection; as such comparisons between impact of tumor downstaging between patients treated with liver resection or transplantation with our data are not possible. Two recent meta-analyses failed to demonstrate survival benefit to neoadjuvant transcatheter arterial chemoembolization prior to resection (4,5); potential roles of other neoadjuvant approaches have not been established. Further prospective investigations of novel targeted therapies and possible use of radiotherapy as neoadjuvant treatment in patients with HCC are desperately needed.

Undoubtedly, tumor biology is a critical factor in patient survival after resection or transplantation for HCC. Majority of patients with HCC have background underlying chronic liver disease including chronic hepatitis and cirrhosis. Chronic liver disease predisposes these patients to significantly higher rates of *de novo* tumorigenesis and HCC recurrence (6,7). Successful tumor downstaging was the best surrogate for favorable tumor biology among transplant recipients in our study. Among patients who had liver resection, greater long-term disease-free survival was associated with younger age, solitary rather than multifocal HCC at the time of resection, lower AFP, and absence of

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cirrhosis. At present, liver transplantation offers the best effective treatment of both, the tumor and underlying chronic liver disease. As the efficacy, ability, and availability of antiviral therapy for hepatitis B and C continue to evolve and become accessible, treatment of background liver disease might decrease the risk of tumor recurrence after liver resection. To date, evidence supporting reduction in tumor recurrence after liver resection and antiviral therapy (either pre- or post-resection) is limited.

Finally, liver donor allocation is extremely important. Both author groups describe significant discrepancies between the number of patients awaiting liver transplantation and liver donor availability. The problem of liver donor shortage is exacerbated outside of the Western world where deceased donor donation and/or availability of transplantation in general (e.g., sub-Saharan Africa) is limited. Solutions are difficult. In theory, a reasonably equitable solution would be liver resection for appropriate candidates followed by salvage transplantation (8,9) in patients with demonstrated favorable disease biology as could be measured by the number of recurrent tumors, presence of microvascular invasion in the resection specimen, disease free interval, eradication of the virus, or other factors. In our study, only 6 patients, among 407 who had recurrence by 5 years, had salvage transplantation. Another strategy might be *ab initio* transplantation for patients with high risk histologic markers identified during pathologic evaluation after initial resection (10).

At present, 5-year patient survival after liver transplantation should exceed 70% (11). Cost of liver transplantation is difficult to ascertain and discuss. One of the most important questions is cost to whom? In the United States, patient cost (arguably the more important of the two costs) is frequently fixed to the costs of deductible and co-insurance. Patients without health insurance are in general not candidates for transplantation. Given cost of healthcare, co-insurance maximums are easily reached with either resection or transplantation. Can the cost of recurrence necessitating further treatment, or no treatment and death, and the cost of immunosuppression for liver transplantation be compared? Societal costs are considerably more nebulous and are directly interwoven with ethics and value judgements. Emerging concept of transplant benefit has the potential to estimate survival advantage of liver transplantation for individual patient with HCC across the Barcelona Clinic Liver Cancer classification spectrum and to improve selection of appropriate candidates for transplantation (12).

Tumor recurrence after liver resection for patients with HCC beyond Milan criteria is high. Professional and societal solutions should aim at ongoing evaluation and expansion of tumor downstaging prior to transplantation and/or resection, identification of factors associated with favorable tumor biology, expansion of post-resection liver transplantation strategies, and improvement in development and use of targeted anti-neoplastic and antiviral therapy.

Acknowledgements

None.

Footnote

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

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Cite this article as: Zaydfudim VM, Chapman WC, Nagorney DM. Challenges in patient selection for liver resection or transplantation in patients with hepatocellular carcinoma beyond Milan criteria. HepatoBiliary Surg Nutr 2017;6(4):287-289. doi: 10.21037/hbsn.2017.07.04

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