Perspective

# Liver transplantation for hepatocellular carcinoma: are international guidelines possible?

**Tammy T. Hshieh[1], Vinay Sundaram[2]**

[1]Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, USA; [2]Department of Medicine and Transplant Institute, Loma Linda University Medical Center, Loma Linda Medical School, USA

*Corresponding to:* Tammy T. Hshieh, MD. Beth Israel Deaconess Medical Center, Lowry Medical Offices Building, 110 Francis Street, Suite #1B, Boston, MA 02215, USA. Email: thshieh@bidmc.harvard.edu.

Submitted Sep 09, 2012. Accepted for publication Oct 09, 2012.
doi: 10.3978/j.issn.2304-3881.2012.10.03
**Scan to your mobile device or view this article at:** http://www.thehbsn.org/article/view/1140/1853

Hepatocellular carcinoma (HCC) is an aggressive malignancy that arises in chronic liver disease. It is currently responsible for over 695,000 deaths internationally every year and its incidence continues to rise as liver cirrhosis and its complications persist as major health problems worldwide (1,2). Liver transplantation is considered a potential cure for HCC because it removes both the tumor and diseased liver at risk of malignant transformation. Initially results from liver transplantation for HCC, however, were disappointing due to high post-operative mortality rates, recurrence rates of up to 80%, and poor long-term survival (3,4). It gradually became apparent that successful liver transplantation for HCC was dependent on careful selection of patients with limited disease (5).

The Milan criteria developed by Mazzaferro *et al.*'s pivotal study in 1996 demonstrated that survival among patients with early HCC who underwent liver transplantation could be comparable to survival among patients transplanted for other reasons (6). Early HCC was determined to be a single lesion ≤5 cm or three lesions all smaller than 3 cm, no evidence of gross vascular invasion, and no regional nodal or distant metastases (6). Liver transplantation for patients within the Milan criteria have yielded a five year survival rate >70% and recurrence rates of 13.5-17% (7). Thus, hepatocellular carcinoma now accounts for 19% of liver transplants in the United States annually. Given the shortage of deceased donor organs and increasing demand, however, there is now a smoldering controversy over the appropriate use of liver transplantation for HCC (8). There are currently no standardized or validated methods for tumor burden control while on the transplant waiting list, surveillance of HCC recurrence post-transplantation, use of living donors in transplantation for HCC, or immunosuppression in the setting of HCC. Furthermore, there is minimal data regarding cost-effective strategies to address these issues, which incur significant expense upon an already taxed healthcare system (9).

Within this context, Clavien *et al.*'s review in the January 2012 issue of Lancet Oncology on liver transplantation for hepatocellular carcinoma is of particular interest. Clavien *et al*. explore these issues in depth and provide specific evidence-based recommendations made by an international committee of experts. On December 2-4, 2010, with the support of ten international hepatology and transplantation societies, a consensus conference was held in Zurich, Switzerland. The goal was to establish evidence-based guidelines for liver transplantation in patients with HCC, to guide liver transplantation programs in their allocations and management of patients pre and post-transplantation. The organizing committee determined key topics and appointed 19 working groups of 4-6 experts to review the evidence available on Pubmed, Embase, Scopus and Cochrane. The experts were selected based on their scientific and clinical merits and drafted recommendations based on their literature review. These drafts are publicly available as supplements through *Liver Transplantation* (10). The chair of each working group gave a 15-minute presentation on their topic and allowed for questions and debate from an audience of 300 participants from five continents. An anonymous audience poll was obtained to determine strength of consensus. Finally, a nine-member jury finalized the recommendations, assigning a level of evidence and strength of evidence grade to each. The review published in Lancet Oncology was prepared by members of the

organizing committee and circulated among all the working groups to ensure accuracy and consensus.

The international consensus conference reports 37 evidence-based guidelines that encompass the following areas: assessment of candidates with HCC for liver transplantation, criteria for listing cirrhotic candidates with HCC, criteria for listing non-cirrhotic candidates with HCC, role of downstaging, managing patients on the waiting list, role of live donor liver transplantation and post-transplant management. Clavien *et al*. review each guideline, referencing the major studies utilized to help formulate the recommendation. Preliminary data from certain studies, which were not incorporated into the recommendations, are also discussed.

HCC needs to be staged as accurately as possible, to predict risk of recurrence post-transplantation and determine the most appropriate treatment option. There are currently several staging systems available, including the Barcelona Clinic Liver Cancer (BCLC) staging system, Tumor Node Metastasis (TNM) system, Cancer of the Liver Italian Program and Japan Integrated Staging Score. However, there is currently no internationally accepted system (11). Thus, the international consensus conference determined that the evidence was strongest for using the BCLC staging to determine prognosis prior to liver transplantation, while the TNM system, which incorporates explant pathology, is best utilized to determine prognosis post-transplant. The BCLC staging system also has the benefit of linking prognosis to treatment recommendations. For tumors greater than 1 cm in size, dynamic CT or MRI demonstrating arterial enhancement followed by washout on portal venous or delayed imaging was felt to be the best non-invasive means of diagnosing and staging HCC pre-operatively. Extrahepatic staging should also include CT scan of the chest and either CT scan or MRI of the pelvis. Because of these advances in imaging technology, liver biopsy is no longer required in the HCC work-up. A positive tumor biopsy rules in the diagnosis but a negative biopsy raises unanswered questions; the procedure itself risks tumor seeding along the needle track (12).

Due to the limited supply of deceased donor livers internationally, fair allocation has raised moral/ethical, medical and even economical questions. The goal is ultimately to justly distribute this limited resource in a way that benefits the most individuals, provides collective benefit, and minimizes consequences for other potential recipients still on the waiting list (13). Thus, the Milan criteria was still felt to be the best standard for selecting HCC patients for liver transplantation, with allowance for expanded criteria acceptance for transplant determined on a program by program basis (6). Alpha-fetoprotein may be used in combination with imaging to guide decision making; however the reviewers felt strongly that there is insufficient evidence to recommend biomarkers other than alpha-fetoprotein be used in clinical decision-making (14). As microvascular invasion cannot be detected prior to liver transplantation, the reviewers strongly recommended against relying on it to determine candidacy for transplant (14). The Milan criteria are not applicable to non-cirrhotics with HCC (15).

Downstaging using regional therapy such as radiofrequency ablation, trans-arterial chemoembolization, or liver resection aims to decrease tumor burden so that patients outside of the Milan criteria have a chance of qualifying for MELD exception points. Upon literature review, the international consensus conference felt that successfully downstaging tumor size or number of viable tumors generally achieves five-year transplantation survival comparable to that of HCC patients who did not require downstaging to meet liver transplantation criteria (16). There is, however, currently not enough evidence to recommend any specific downstaging therapy over the others (16).

Waiting lists for organ donation are inherently dynamic, as patients clinically improve or worsen. Thus, the international consensus conference recommended periodic monitoring of waiting lists via imaging and alpha-fetoprotein measurements. Understandably, there is good evidence to suggest that patients who have progressed beyond liver transplantation criteria should be placed on hold and considered for downstaging, with ultimate removal from the waiting list if no longer candidates (17).

Standardized guidelines for post-transplant surveillance of HCC recurrence after liver transplantation are lacking, perhaps due to the relative rarity of recurrence (18). The international consensus committee was only able to weakly recommend, upon review of the evidence, that patients undergo contrast CT or MRI imaging plus alpha-fetoprotein measurements 6-12 months post-operatively (9). Furthermore, there is inadequate evidence to recommend any specific immunosuppression regimen or adjuvant antitumor therapy to decrease the chances of HCC recurrence. The primary consensus was that recurrence is best treated with regional therapy or sorafenib, and that liver re-transplantation would not be appropriate (19).

Clavien *et al*.'s review of recent international consensus is comprehensive and useful, but care must be taken in

 

interpretation of these recommendations. They raise the question of whether international guidelines are feasible given significant regional variability. It should be noted that of the 37 guidelines, the level of evidence for fourteen were based on case series/expert opinions and the strength of recommendation for fifteen were weak. The international consensus conference also yielded some obvious recommendations, such as patients who fall outside of Milan criteria should not be transplanted. Other recommendations were vague and subjective (ex: liver donor transplants should only occur at centers of excellence). Furthermore, can these guidelines be effectively disseminated? Knowledge translation in healthcare is important but often challenging (20). It has been two years since these international consensus guidelines were released and how widely they have been accepted remains subjective and debatable.

Nevertheless, this review highlights the central role of expert discussion and consensus – working in combination with evidence-based medicine – to guide better care for complex patients. Clavien *et al*. address for the first time some controversial topics surrounding liver transplantation in a collegial and academic approach. The recommendations are helpful in that they were deliberately phrased flexibly while still providing data-supported, expert guidance. This permits adjustments by programs based on their regional circumstances, team experiences and the unique characteristics of local waiting lists, donor organ availabilities.

Clavien *et al*. raise intriguing questions with respect to liver transplantation that need to be more carefully evaluated. Although the number of weak and non-applicable recommendations was high, this highlights areas that need further research. This review will potentially stimulate future exploration into areas such as microvascular invasion, liver tumor markers beyond alpha-fetoprotein, specific downstaging therapies, and ideal surveillance intervals. The recommendations made by the international consensus conference are an encouraging step in the right direction and will hopefully spark the development of more effective guidelines as well as treatment options to optimize our approach to HCC.

## Acknowledgements

*Disclosure:* The authors declare no conflict of interest.

## References

1. 2009 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1994-2009. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD; United Network for Organ Sharing, Richmond, VA; University Renal Research and Education Association, Ann Arbor, MI.
2. Sherman M, Peltekian KM, Lee C. Screening for hepatocellular carcinoma in chronic carriers of hepatitis B virus: incidence and prevalence of hepatocellular carcinoma in a North American urban population. Hepatology 1995;22:432-8.
3. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. Surgery 1991;110:726-34; discussion 734-5.
4. 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.
5. Iwatsuki S, Starzl TE, Sheahan DG, et al. Hepatic resection versus transplantation for hepatocellular carcinoma. Ann Surg 1991;214:221-8; discussion 228-9.
6. 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:S44-57.
7. Prasad KR, Young RS, Burra P, et al. Summary of candidate selection and expanded criteria for liver transplantation for hepatocellular carcinoma: a review and consensus statement. Liver Transpl 2011;17:S81-9.
8. Poon RT, Fan ST, Lo CM, et al. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 2002;235:373-82.
9. Chan EY, Larson AM, Fix OK, et al. Identifying risk for recurrent hepatocellular carcinoma after liver transplantation: implications for surveillance studies and new adjuvant therapies. Liver Transpl 2008;14:956-65.
10. Lesurtel M, Clavien PA. 2010 International Consensus Conference on Liver Transplantation for Hepatocellular Carcinoma: texts of experts. Liver Transpl 2011;17:S1-5.
11. Wildi S, Pestalozzi BC, McCormack L, et al. Critical evaluation of the different staging systems for hepatocellular carcinoma. Br J Surg 2004;91:400-8.
12. Silva MA, Hegab B, Hyde C, et al. Needle track seeding following biopsy of liver lesions in the diagnosis of

 

hepatocellular cancer: a systematic review and meta-analysis. Gut 2008;57:1592-6.
13. Toso C, Asthana S, Bigam DL, et al. Reassessing selection criteria prior to liver transplantation for hepatocellular carcinoma utilizing the Scientific Registry of Transplant Recipients database. Hepatology 2009;49:832-8.
14. Villanueva A, Hoshida Y, Toffanin S, et al. New strategies in hepatocellular carcinoma: genomic prognostic markers. Clin Cancer Res 2010;16:4688-94.
15. Houben KW, McCall JL. Liver transplantation for hepatocellular carcinoma in patients without underlying liver disease: a systematic review. Liver Transpl Surg 1999;5:91-5.
16. Ravaioli M, Grazi GL, Piscaglia F, et al. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. Am J Transplant 2008;8:2547-57.
17. Majno P, Lencioni R, Mornex F, et al. Is the treatment of hepatocellular carcinoma on the waiting list necessary? Liver Transpl 2011;17:S98-108.
18. Zimmerman MA, Ghobrial RM, Tong MJ, et al. Recurrence of hepatocellular carcinoma following liver transplantation: a review of preoperative and postoperative prognostic indicators. Arch Surg 2008;143:182-8;discussion 188.
19. Hollebecque A, Decaens T, Boleslawski E, et al. Natural history and therapeutic management of recurrent hepatocellular carcinoma after liver transplantation. Gastroenterol Clin Biol 2009;33:361-9.
20. Pronovost PJ, Berenholtz SM, Needham DM. Translating evidence into practice: a model for large scale knowledge translation. BMJ 2008;337:a1714.

**Cite this article as:** Hshieh TT, Sundaram V. Liver transplantation for hepatocellular carcinoma: are international guidelines possible? Hepatobiliary Surg Nutr 2013;2(2):113-116. doi: 10.3978/j.issn.2304-3881.2012.10.03

 