EDITORIAL

Towards More Effective Liver Allocation Criteria for Hepatocellular Carcinoma: Tumor Response to Locoregional Therapy

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Since the United Network of Organ Sharing (UNOS) implemented the Milan criteria in 2002 to assign listing priorities for liver transplantation in patients with hepatocellular carcinoma (HCC), the field of liver transplantation has actively searched for further refinements to optimize organ allocation for this indication.¹ The success of the Milan criteria lies not only in its ability to stratify patients by their long-term outcomes after liver transplantation for HCC but in its ease of application: on preoperative cross-sectional imaging, patients with cirrhosis and a single tumor smaller than 5 cm or up to three tumors each smaller than 3 cm without macrovascular invasion or extrahepatic spread receive transplantation priority. Numerous studies have subsequently reported that liberalization of these thresholds on tumor size and number results in similar long-term outcomes and have begun to influence prioritization schemes; for example, the Transplantation Society of Australia and New Zealand has moved to using the University of California, San Francisco (UCSF) criteria, defined as a single tumor up to 6.5 cm in diameter or three tumors with total tumor diameter up to 8 cm.² Application of either the Milan or UCSF criteria results in an appreciable HCC recurrence rate of approximately 10% at 5 years. That the liberalization of prioritization criteria can produce comparable long-term results but continues to result in a measurable rate of cancer recurrence indicates that there exist larger tumors which may have favorable biology and may be cured with transplantation, whereas some diminutive lesions may be biologically aggressive and have higher chance of recurrence after transplantation.

The task at hand is to develop better indicators to select patients with lower likelihood of HCC recurrence after transplantation.

Numerous efforts have investigated the use of molecular assays to stratify patients. For example, Dvorchik et al. found in a study of 183 patients that those who had tumors with a fractional allelic imbalance (FAI) rate across nine microsatellite markers—a proxy for the cumulative mutation damage within a tumor—of >40% had recurrence risk increased by a factor of 19.5 compared with those with FAI of ≤20%.³ In a study seeking to find a serum marker to predict the presence of microvascular invasion by tumor, which is associated with greatly increased chance of HCC recurrence after transplantation, Shirabe et al. found serum des-gamma-carboxy prothrombin levels to have 75% sensitivity and 85% specificity in predicting this invasion.⁴

Clinical indicators have the benefit of being more accessible and readily applied in the preoperative phase. One clinical indicator which may reflect the biology of individual tumors is the response of the tumor to locoregional therapy such as transarterial chemoembolization (TACE) and radiofrequency ablation therapy prior to transplantation. Otto et al. found that 39 patients who received TACE and whose tumors did not progress while awaiting transplant were 95% recurrence free with 5-year follow-up.⁵ In comparison with the Milan criteria, absence of tumor progression after TACE was found to be a better predictor of recurrence-free survival. This study used size measurements from serial contrast spiral computer tomography (CT) scans to monitor tumor progression after TACE. Possibly a more meaningful assessment of tumor response would be to quantitate the amount of residual viable tumor after treatment. At our institution, 16 patients who received pretransplant locoregional therapy and who

were found to have complete pathologic response within the explanted liver had no episodes of recurrence with 5-year follow-up.⁶ In this regard, we believe that pre-transplant TACE has oncologic benefit beyond that provided as a “bridge” to transplant in wait-listed patients. However, no prospective randomized trials have been conducted to answer this question definitively.

Although it seems intuitive that complete pathologic responses to locoregional therapies result in favorable outcomes, might gradations of partial responses to locoregional therapy be a useful predictor of HCC recurrence after transplant? In this issue of *Annals of Surgical Oncology*, Chan et al. take a step towards addressing this question.⁷ Eighty-two patients, 23 of whom had tumors beyond UCSF criteria, were followed after locoregional therapy. Eighty percent of patients received TACE, and the remainder were treated with local ablation. Mean follow-up was 30.7 months after transplantation; 15.8% of the patients were found to have HCC recurrence. Clinicopathologic factors encompassing demographics, laboratory values, and pathologic tumor characteristics were used in multivariate analysis to determine prognostic factors of HCC recurrence. The only independent factor associated with lower HCC recurrence was mean tumor necrosis $\geq 60\%$ after locoregional therapy, which represents an incremental refinement in our knowledge of locoregional therapy and transplant outcomes for HCC. These results suggest that a decrement in the amount of viable tumor as assessed by pathology may prognosticate better than clinicopathologic factors previously associated with recurrence-free survival, including the components of the Milan or UCSF criteria, tumor grade, and microvascular invasion.

How does this inform our current schema of HCC prioritization for transplantation? Chan et al. further stratify patients within and beyond UCSF criteria by their response to locoregional therapy: In 59 patients who met UCSF criteria prior to locoregional therapy, the 37 who had $\geq 60\%$ mean tumor necrosis had 92% recurrence-free survival at 5 years, whereas the remaining 22 with $<60\%$ mean tumor necrosis were 68% recurrence free. In 23 patients beyond UCSF criteria prior to locoregional therapy, the 11 patients who were able to be downstaged to within UCSF criteria with locoregional therapy were 91% recurrence free at 5 years, whereas those who did not meet this response threshold were 33% recurrence free. An intriguing question not explicitly addressed in this study is how the outcomes of the 11 patients downstaged into UCSF criteria compare with those originally within UCSF criteria; the 91% recurrence-free survival of these 11 patients is nominally better than the 68% recurrence-free survival of the 22 patients who were within UCSF criteria and had $<60\%$ mean tumor necrosis. It is unclear if these results give us a glimpse of the answer to the controversial

topic of whether patients outside of Milan/UCSF criteria who exhibit significant tumor response to locoregional therapy would be expected to fare better than patients who start within Milan/UCSF criteria but have a lesser response to locoregional therapy.

One barrier to using tumor response in a prioritization scheme is the ability to assess this response accurately. The current scheme used by UNOS relies on radiographic measurements of tumor size. In recent studies addressing the effect of locoregional therapy on transplantation outcomes, inconsistent methods of radiographic assessment of response have been used: Chapman et al. assessed response using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines^{8,9}; Ravaioli et al. used radiologic evidence of viable tumor to assess tumor number but did not distinguish between nonviable versus viable tumor in measuring tumor size¹⁰; and Yao et al. used viable tumor diameter for radiologic measurements.¹¹ Furthermore, Hunt et al. reported low accuracy of radiographic assessment of tumor viability at their institutions.¹² Clearly, a uniform, accurate, and preferably noninvasive assessment of tumor response to locoregional therapy will need to be agreed upon by the transplantation community prior to its incorporation into any prioritization scheme.

These results from Chan et al. provide leads for future investigations into continued questions about the role of locoregional therapy and transplantation for HCC. With rising incidence of HCC and with 70% of patients presenting beyond Milan criteria, the ability to better select for patients who would derive long-term survival after transplantation would benefit the community of people who seek to benefit from liver transplantation.

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REFERENCES

1. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *New Engl J Med*. 1996;334(11):693–700.
2. Yao FY, Xiao L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. *Am J Transplant*. 2007;7(11):2587–96.
3. Dvorchik I, Schwartz M, Fiel MI, Finkelstein SD, Marsh JW. Fractional allelic imbalance could allow for the development of an equitable transplant selection policy for patients with hepatocellular. *Transplantation*. 2008;14:443–50.
4. Shirabe KEN, Itoh S, Yoshizumi T, Soejima Y. The predictors of microvascular invasion in candidates for liver transplantation with hepatocellular carcinoma—with special reference to the serum levels of des-gamma-carboxy prothrombin. *J Surg Oncol*. 2007;95:235–40.

5. Otto G, Herber S, Heise M, et al. Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. *Transplantation*. 2006;12:1260–7.
6. Bharat A, Brown DB, Crippin JS, et al. Pre-liver transplantation locoregional adjuvant therapy for hepatocellular carcinoma as a strategy to improve longterm survival. *J Am Coll Surg*. 2006; 203(4):411–20.
7. Chan KM, Yu MC, Chou HS, et al. Significance of tumor necrosis on the outcome of patients with hepatocellular carcinoma receiving locoregional therapy prior to liver transplantation. *Ann Surg Oncol*. 2011.
8. Chapman WC, Majella Doyle MB, Stuart JE, et al. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. *Ann Surg*. 2008;248(4):617–25.
9. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment. *J Natl Cancer Inst*. 2000; 92(3):205–16.
10. 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(12):2547–57.
11. Yao FY, Kerlan RK, Hirose R, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. *Hepatology*. 2008;48(3): 819–27.
12. Hunt SJ, Yu W, Weintraub J, Prince MR, Kothary N. Radiologic monitoring of hepatocellular carcinoma tumor viability after transhepatic arterial chemoembolization: estimating the accuracy of contrast-enhanced cross-sectional imaging with histopathologic correlation. *J Vasc Interv Radiol*. 2009;20(1):30–8.