EDITORIAL

Tumor Size Remains Key for Prediction of Hepatocellular Carcinoma Recurrence after Liver Transplantation

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Resection remains the mainstay of therapy for hepatocellular carcinoma (HCC) in patients without chronic liver disease and in selected patients with well-compensated liver injury. Even when resection can be successfully performed, this treatment strategy is plagued by excessive recurrence risk in the remnant liver with 5-year disease-free survival rates of only 20–30%.¹ Many patients have advanced liver disease and/or multicentric tumors and therefore undergo liver transplantation as their only curative option. Outcomes with liver transplantation for appropriately selected candidates are excellent with 5-year recurrence-free survival of approximately 70%.² Because of high recurrence rates for patients with more advanced stage tumors, transplantation is (in most centers) restricted to those patients who have early-stage disease. Several groups have been able to show that with the use of neoadjuvant treatment, such as TACE, good outcomes are possible for a significant percentage of patients with tumors outside of the Milan criteria.^{3,4} Still, the majority of patients continue to present with advanced disease and the minority, albeit a significant portion, can be downstaged.

Using the strict limitations imposed by Milan criteria, recurrence after transplantation in most series is 10%.² Moreover, as discussed above, there are a significant portion of patients outside of these criteria in whom good outcomes with liver transplantation can be obtained. This indicates that the use of size as a surrogate of tumor biology or aggressiveness is crude at best. Because of this, there is great interest in fine tuning our ability to predict recurrence by quantifying tumor behavior on the genetic or protein level. In the current report, Yang et al. present an analysis of 60 patients who have undergone liver

transplantation for HCC. Tumor expression of the long intervening non-coding RNA, HOTAIR, was analyzed as a correlate of recurrence using both univariate and multivariate methods. This particular lincRNA has been shown to strongly correlate with metastasis and recurrence-free survival in patients with breast cancer.⁵ The authors found that HOTAIR expression is higher in tumors compared with adjacent nontumor liver, and HOTAIR expression is significantly associated with recurrence after liver transplantation in both uni- and multivariate analysis. The vast majority (45/60, 75%) of patients included in the study had tumors that exceeded Milan criteria and 20 of 60 had portal vein tumor thrombus. As expected with a substantial portion of advanced tumors, there is a very high rate of recurrence (35/60, 58.3%). Even for patients meeting Milan criteria, tumors recurred in 4 of 15 (26.7%)—a number in excess of most series. As has been validated in numerous other studies, patients who exceeded Milan had significantly worse recurrence-free survival than those within the criteria (Table 2). In patients with tumors exceeding Milan, increased HOTAIR expression was associated with earlier recurrence (Fig. 1c). In multivariate analysis, HOTAIR expression, tumor size, and AFP levels are all significant predictors of recurrence; however, results are not provided for the role of Milan status, the presence of tumor thrombus, or tumor multicentricity—all factors known to be strongly correlated with disease recurrence after transplantation.

The overall sensitivity and specificity of HOTAIR in this cohort is 65 and 64%, respectively. If HOTAIR were utilized as a selection criteria for transplantation, 28 of 60 (46.7%) would have been transplanted. Fifteen of 60 (25%) who did not experience recurrence would not have been eligible for transplant. Of those who would receive a transplant, 12 of 28 (42.9%) would experience recurrence. For those inside of the Milan criteria, 5 of 15 (33.3%) are eligible for transplant, although no recurrence was noted in

this cohort (0/5). Outside of Milan criteria, 31 of 45 (68.9%) patients recurred regardless of HOTAIR status. Use of HOTAIR would have reduced this number to 11 of 23 (47.8%). Two-year recurrence-free survival for patients outside of Milan is approximately 40% vs. <20% with low and high tumor HOTAIR expression respectively. These results give pause when considering expansion of the Milan criteria and utilization of deceased donor organs for HCC. However, if HOTAIR is to be utilized as a selection tool for organ allocation for patients outside of Milan, then significantly lower recurrence rates, as in other series, will need to be documented before its application.

Utilization of HOTAIR as a preoperative predictor of recurrence would require tumor biopsy that is not currently necessary for diagnosis and listing for transplant. It is possible that preoperative tumor biopsy could be added for improved prognostication of HCC, although the authors need to demonstrate that this will have the same predictive value as is suggested in the current report where the whole liver explant was available for analysis. Biopsy has the potential to improve patient selection from the current, rudimentary size-based approach; this improvement will initially come from analysis of numerous genetic changes present within the tumor as is utilized in other solid tumors.⁶ Perhaps the most interesting application using HOTAIR could be for patient selection for adjuvant therapy after resection or transplantation. The authors have shown that HOTAIR is associated with invasion and/or metastasis in several HCC cell lines and this phenomenon has been well documented in breast cancer.⁵

Because of the large discrepancy between supply and demand of deceased donor liver allografts, recurrence rates after liver transplantation for HCC must be low. Therefore, studies to determine changes in outcome will require large sample sizes to detect subtle differences. The study in this

issue documents a significant association between HOTAIR expression and HCC recurrence after liver transplantation. However, the recurrence rates in this report are exceptionally high, likely due to the advanced-stage tumors present in many patients. Larger-scale investigation is necessary to determine whether HOTAIR expression is associated with recurrence for patients within Milan before it can be prospectively applied to those patients who exceed the criteria. The article in this issue, however, does represent another step toward better biologic quantification of tumor behavior.

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REFERENCES

1. Ercolani G, Grazi GL, Ravaioli M, et al. Liver resection for hepatocellular carcinoma on cirrhosis: univariate and multivariate analysis of risk factors for intrahepatic recurrence. *Ann Surg.* 2003;237(4):536–43.
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(11):693–9.
3. Yao FY, Xiao L, Bass NM, Kerlan R, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. *Am J Transplant.* 2007;7(11):2587–96.
4. 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.
5. Gupta RA, Shah N, Wang KC, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature.* 2010;464(7291):1071–6.
6. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med.* 2004;351(27):2817–26.