



Improving predictive performance of selection criteria for liver transplantation with hepatocellular carcinoma: combining morphological and biomarker criteria

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Liver transplantation (LTx) has become well established internationally as the best treatment option for patients with small unresectable hepatocellular carcinomas (HCC). Our impact and effectiveness in utilizing LTx in the treatment of HCC has been limited mainly by donor availability and by our (in)ability to select the appropriate candidates. This has included both errors of omission (where candidates that may have expected a reasonable long-term survival were ruled out for transplant) and commission (where patients with advanced and/or aggressive tumors have been transplanted only to experience early recurrence and short survival). Initial problems with near open candidacy for HCC in the 1980's led to poor outcomes (1) and a veritable moratorium that was reversed largely by Mazzaferro's report of excellent outcomes in a population with tumors tightly selected by size and number (2). Low rates of tumor recurrence, thanks to tight selection with Milan criteria, in a patient group that usually has a low natural MELD (model for end-stage liver disease) score provides excellent survivals, but is now recognized to exclude from transplant candidacy a significant number of patients that might expect more than satisfactory survivals after LTx for more advanced HCC.

A series of important papers have been published reporting good post-transplant results in patient groups that were characterized by an expansion of the morphological criteria of tumor size and number in the Milan criteria (3-6). Perhaps not surprisingly, as in other areas of oncology,

the impact of both tumor staging and grading (degree of differentiation) have become increasingly apparent over time. The importance of markers of aggressive tumor biology in predicting higher rates of tumor recurrence and poor survival have included such factors as microvascular invasion (7), tumor grade on explant pathology (8), as well as serum biomarkers such as alpha-fetoprotein (AFP) (3), des-gamma-carboxy prothrombin (DCP/PIVKA II) (9,10), and lens culinaris agglutinin A-reactive fraction of AFP (AFP-L3) (11). Ease of assay on serum and widespread availability have allowed extensive evaluation and increasing application of AFP in this role. Information that is only available from post-transplant pathology logically cannot be used for candidate selection and the potential morbidity of pre-transplant biopsy has discouraged broad adoption of other such histologically based biological markers.

Our analysis of factors associated with patient survival after LTx for HCC in the scientific registry of transplant recipients was the first to report that morphological factors [represented by total tumor volume (TTV) of <115 cm³] and biomarkers (represented by AFP <400 ng/mL) were independent predictors of outcome and that a combination of both outperformed Milan and UCSF (University of California, San Francisco) criteria (12). Our initial report has been supported and extended by the recently published outcomes of a prospective multicenter study on the application of the composite TTV/AFP selection

criteria for LTx with HCC. Overall HCC recurrence rate in a consecutive series of 166 patients transplanted in three centers in Canada and Switzerland was 5.4% (9 of 166), including 6 of 134 patients (4.5%) within Milan by morphological assessment and 3 of 32 (9.4%) beyond Milan (13). Recurrence-free survival at 4 years did not differ between the two groups ($86.1\% \pm 3.5\%$ vs. $83.4\% \pm 3.8\%$, $P=0.932$). In 2012, Duvoux *et al.* first reported their findings from prospective study of a large series of LTx patients from France where a model including AFP improved the performance of the Milan criteria for both prediction of tumor recurrence and improved survival (14). A multicenter cohort study from Latin America recently provided additional support for the combining of AFP with morphological criteria in the AFP model (15).

Of interest, an analysis of results from UCSF with 211 consecutive patients within Milan criteria led to the suggestion that inclusion of an AFP cutoff of 1,000 ng/mL in the selection criteria could lead to reduction of HCC recurrence and improved 5-year disease-free survival after LTx (16).

The report by Notarpaolo *et al.* in J Hepatol (17) provides further support for a composite selection criteria from retrospective analysis of an independent patient population in Italy where viral hepatitis represented the underlying pathology to HCC in >80% of patients. Combining morphological and biomarker factors again outperformed Milan criteria in prediction of recurrence rate and patient survival. AFP was found to be a surrogate for both tumor differentiation and microvascular invasion in explant pathology evaluation. As predicted by the AFP model, high AFP correlated with increased recurrence rates and reduced survivals.

Where do we see the current state of selection criteria for LTx in patients with HCC? An increasing body of literature supports the addition of AFP as a biomarker to improve prediction of established morphological criteria. Such composite criteria are now established as national criteria in France and Canada. Many questions remain. What impact might such changes have on other LTx candidates on the waitlist, including non-tumor patients and HCC patients within Milan? The expansion of candidacy with broadened morphological criteria whether TTV or UCSF-like appears to be about 30%, an impact that is tempered by an approximate 10% reduction secondary to application of AFP limits (17,18). While a 20% increase in candidacy will be expected to lengthen wait-times for all, it seems unfair

to consider continuing to deny candidacy to such expanded HCC patients where multiple programs from several countries on three continents have now demonstrated 5-year survival numbers above 70%.

Do we see advantages of one system or another that would support further adoption? The AFP model could be simplified for bedside application by distilling it to its essence—what are the situations where factors yield a score >2:

- (I) Largest tumor diameter >6 cm;
- (II) AFP > 1,000 ng/mL;
- (III) Any 2 of: tumor >3 cm, >3 tumors, AFP > 100 ng/mL.

Will the AFP model achieve better outcomes from subtle differences in patients with mid-range risk of both tumor size/number and AFP, where the TTV/AFP criteria utilizes two hard endpoints? Or do the ranges involved prove a disadvantage? Does utilization of TTV as a better representation of the mass of cancer (akin to AFP level) provide more accurate prediction of recurrence risk that a one-dimensional assessment by diameter? Is the increased impact of large tumors on volume and the parallel improvement in radiological prediction with TTV more important than additional numbers of small tumors in the AFP model? Consider 2 patients:

- (I) Three tumors of 3 cm (TTV, 42.4 cm³) and an AFP of 975 ng/mL;
- (II) Four tumors of 1 cm (TTV, 2.1 cm³) and an AFP of 110 ng/mL.

The first patient qualifies under the AFP model (and the updated UCSF model), but not under the TTV/AFP. The second patient is excluded under AFP model (and UCSF), but remains a candidate with TTV/AFP. With 20-fold greater tumor mass and 9-fold higher AFP, it would seem the first patient has a substantially higher risk for recurrence.

We are in agreement with the summary from Notarpaolo *et al.* (17): Only by analysis of additional and larger well-structured prospective series will we be able to provide the data to allow accurate ongoing refinement of our HCC candidate selection criteria.

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Footnote

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References

- McPeake JR, O'Grady JG, Zaman S, et al. Liver transplantation for primary hepatocellular carcinoma: tumor size and number determine outcome. *J Hepatol* 1993;18:226-34.
- 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.
- Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001;33:1394-403.
- 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;7:2587-96.
- Toso C, Trotter J, Wei A, et al. Total tumor volume predicts risk of recurrence following liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl* 2008;14:1107-15.
- Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009;10:35-43.
- Bhattacharjya S, Bhattacharjya T, Quaglia A, et al. Liver transplantation in cirrhotic patients with small hepatocellular carcinoma: an analysis of pre-operative imaging, explant histology and prognostic histologic indicators. *Dig Surg* 2004;21:152-9; discussion 159-60.
- Decaens T, Roudot-Thoraval F, Bresson-Hadni S, et al. Role of immunosuppression and tumor differentiation in predicting recurrence after liver transplantation for hepatocellular carcinoma: a multicenter study of 412 patients. *World J Gastroenterol* 2006;12:7319-25.
- Fujiyama S, Morishita T, Hashiguchi O, et al. Plasma abnormal prothrombin (des-gamma-carboxy prothrombin) as a marker of hepatocellular carcinoma. *Cancer* 1988;61:1621-8.
- Weitz IC, Liebman HA. Des-gamma-carboxy (abnormal) prothrombin and hepatocellular carcinoma: a critical review. *Hepatology* 1993;18:990-7.
- Yamashita F, Tanaka M, Satomura S, et al. Prognostic significance of Lens culinaris agglutinin A-reactive alpha-fetoprotein in small hepatocellular carcinomas. *Gastroenterology* 1996;111:996-1001.
- 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.
- Toso C, Meeberg G, Hernandez-Alejandro R, et al. Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: A prospective validation. *Hepatology* 2015;62:158-65.
- Duvoux C, Roudot-Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including α -fetoprotein improves the performance of Milan criteria. *Gastroenterology* 2012;143:986-94.e3; quiz e14-5.
- Piñero F, Tisi Baña M, de Ataíde EC, et al. Liver transplantation for hepatocellular carcinoma: evaluation of the alpha-fetoprotein model in a multicenter cohort from Latin America. *Liver Int* 2016;36:1657-67.
- Hameed B, Mehta N, Sapisochin G, et al. Alpha-

fetoprotein level > 1000 ng/mL as an exclusion criterion for liver transplantation in patients with hepatocellular carcinoma meeting the Milan criteria. *Liver Transpl* 2014;20:945-51.

17. Notarpaolo A, Layese R, Magistri P, et al. Validation of the AFP model as a predictor of HCC recurrence in patients

with viral hepatitis-related cirrhosis who had received a liver transplant for HCC. *J Hepatol* 2017;66:552-9.

18. Toso C, Kneteman NM, James Shapiro AM, et al. The estimated number of patients with hepatocellular carcinoma selected for liver transplantation using expanded selection criteria. *Transpl Int* 2009;22:869-75.

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