



Liver Transplantation as Cure of Hepatocellular Carcinoma: It is not a Matter of Time, it is a Matter of Tumor Biology

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Hepatocellular carcinoma (HCC) is the third most common cause of cancer mortality world-wide. Despite the success in the treatment of hepatitis C and the reduction of hepatitis B in Asia due to immunization programs the incidence of HCC will increase in Europe, North and Southamerica and Asia.^{1,2} This trend is due to the dramatic increase in Non-alcoholic fatty liver disease (NAFLD/ NASH), which is becoming more and more important in the development of HCC.³ Disease related mortality of HCC is still high, since curative treatment options beside resection and liver transplantation (LT) are lacking. In patients with advanced liver disease and cirrhosis LT is the only curative option. Limitations of treating HCC with LT are the risk of tumor recurrence after LT and the relative organ shortage which causes a competition for organs between patients with HCC and non-malignant end stage liver diseases.

1996 Mazzaferro, *et al.* defined size criteria for HCC-patients suitable for LT (Milan-criteria),⁴ which were extended by the UCSF group in 2001 (San-Francisco-criteria).⁵ Both criteria were based on size and number of individual HCC-nodules in the liver. Organ allocation was switched to the MELD system in the most countries in 2002 and 2003, which raised the question how to deal with HCC patients waiting for a transplant with good liver function and consecutively low MELD. Extrapoints (exceptional MELD) were introduced to deal with this issue. First the points were allocated adjusted to an estimated three-months mortality causing a disadvantage for patients with non-malignant liver diseases. The system was modified over time successive increasing the waiting time for patients with HCC in order to overcome a disadvantage for patients with non-malignant liver disease.⁶

It is not clear how the increase in waiting list will influence the recurrence free survival rate after LT for pa-

tients with HCC. Palmer, *et al.* reported in this issue of *Annals of Hepatology* the impact of waiting time on recurrence free survival in a large single center retrospective analysis.⁷ Interestingly, they did not find any impact of waiting time on recurrence free survival. Indeed, 90% of the patients initially enrolled for LT for HCC received a LT and only 5% were excluded due to progress. The drop-out rate increased over waiting time to reach 6 % at six months, 15% at one year 42% at two years. Regarding patients after LT the authors did not find any differences in recurrence free survival and/or overall in patients waiting more or less than 180 days. Moreover, therapeutic local ablative interventions like RFA and TACE or both in order to downstage the tumor did not influence recurrence rate after LT. The factors influencing the recurrence rate were explant vascular invasion, tumor grade and AFP. Explant vascular invasion and AFP influenced also overall survival.

First conclusion of the work of Palmer, *et al.* is that successful LT for HCC is rather more dependent on tumor biology than on the waiting time on the transplant list. This leads to the second conclusion that we might have to improve our pre-LT diagnostic work-up to identify patients at risk.

For the AFP the author found that an elevated AFP or quickly rising AFP above 400 ng/mL was associated with recurrence. AFP is already included in most diagnostic work-up of HCC on the waiting list and should be monitored carefully. More difficult to evaluate is vascular invasion at the time of transplantation. The authors did not analyze the impact of micro- or macrovascular invasion, however it is clear that there must be a focus on pre-transplant diagnostic and surveillance. Modern imaging tools like MRI and vascular ultrasound might be helpful. Tumor grading was the third predictive factor in this study.

Grading as a prognostic tool leads us to the question of biopsy for HCC. Most diagnostic guideline does not require biopsy for the diagnosis of HCC especially in cirrhotic patients.^{8,9} The sensitivity and specificity of MRI, contrast enhanced ultrasound and CT-Scan are high especially in larger nodules. Smaller nodules are challenging for biopsies and there is a very low risk (1-2%) for implantation metastases¹⁰ which can be reduced by technical improvements.¹¹ On the other hand histopathological examination and grading, and genomics and/or proteomics will be of importance in the future not only for identification of patients suitable for LT but also for identifying candidates for targeted therapies.¹¹ Liquid biopsies may be an alternative for the future, however the technique for HCC is still in early stages of development.¹²

In conclusion the important paper of Palmer, *et al.* underscores the tumor biology in course of HCC recurrence after LT. It is therefore important to focus the future research on biomarkers for HCC, which may establish more individualized criteria for patients with HCC who are considered for LT.

REFERENCES

1. Seyda Seydel G, Kucukoglu O, Altinbasv A, Demir OO, Yilmaz S, Akkiz H, Otan E, et al. Economic growth leads to increase of obesity and associated hepatocellular carcinoma in developing countries. *Ann Hepatol* 2016; 15: 662-72.
2. Bertuccio P, Turati F, Carioli G, Rodriguez T, La Vecchia C, Malvezzi M, Negri E. Global Trends and Predictions in Hepatocellular Carcinoma Mortality. *J Hepatol* 2017.
3. Ertle J, Dechene A, Sowa JP, Penndorf V, Herzer K, Kaiser G, Schlaak JF, et al. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. *Int J Cancer* 2011; 128: 2436-43.
4. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; 334: 693-9.
5. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology*. 2001;33:1394-403. doi: 10.1053/jhep.2001.24563. PubMed PMID: 11391528.
6. Heimbach JK, Hirose R, Stock PG, Schladt DP, Xiong H, Liu J, Olthoff KM, et al. Delayed hepatocellular carcinoma model for end-stage liver disease exception score improves disparity in access to liver transplant in the United States. *Hepatology* 2015; 61: 1643-50.
7. Palmer WC, Burns J, Croome K, Rosser B, Patel T, Keaveny A, Pungpapong S, et al. Liver Transplantation for Hepatocellular Carcinoma: Impact of Wait Time at a Single Center. *Ann Hepatol* 2017; 16.
8. Bruix J, Sherman M. Diagnosis of Small HCC. *Gastroenterology* 2005; 129: 1364.
9. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; 35: 421-30.
10. Wang P, Meng ZQ, Chen Z, Lin JH, Ping B, Wang LF, Wang BH, et al. Diagnostic value and complications of fine needle aspiration for primary liver cancer and its influence on the treatment outcome-a study based on 3011 patients in China. *Eur J Surg Oncol* 2008; 34: 541-6.
11. Wee A. Fine needle aspiration biopsy of hepatocellular carcinoma and hepatocellular nodular lesions: role, controversies and approach to diagnosis. *Cytopathology* 2011; 22: 287-305.
12. Yin CQ, Yuan CH, Qu Z, Guan Q, Chen H, Wang FB. Liquid Biopsy of Hepatocellular Carcinoma: Circulating Tumor-Derived Biomarkers. *Dis Markers* 2016; 2016: 1427849.

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