Liver transplantation for hepatocellular carcinoma in non-cirrhotic livers regardless of the number and size of tumours?

Thomas Decaens1,2,3,*, Alexis Laurent2,3,4, Alain Luciani2,3,5

1AP-HP, Groupe Hospitalier Henri Mondor, Department of Hepatology, Creteil, France; 2INSERM U955, Creteil, France; 3Université Paris Est Creteil, Faculté de Médecine, Creteil, France; 4AP-HP, Groupe Hospitalier Henri Mondor, Department of Surgery, Creteil, France; 5AP-HP, Groupe Hospitalier Henri Mondor, Department of Radiology, Creteil, France

Hepatocellular carcinoma (HCC) is a major health problem worldwide [1], which continues to increase because of viral hepatitis B and C epidemics, but also because of alcoholic [2] and non-alcoholic liver disease. HCC develops mainly in cirrhotic livers (85–95%). In other cases, the surrounding liver is diseased and fibrous, though in some cases, the surrounding liver can be normal.

In contrast to HCC associated with the cirrhotic liver, non-cirrhotic HCC (NC-HCC) predominantly occurs in young and healthy females with a peak incidence in the fourth decade. NC-HCCs are frequently diagnosed at a late stage, with large tumours (8–14 cm in many series). The preserved liver function allows extensive liver resections: up to 80% of the normal functional liver volume. The 5-year overall survival rates after liver resection for NC-HCC range from 25% to 81% with a tumour-recurrence rate of 30–73% [3]. Liver resection, thus, is currently the best first-line therapy for NC-HCC. However, the use of liver transplantation (LT) in this setting has been recently discussed in connection with unresectable HCC or because of tumour recurrence following initial resection.

In HCC that occurs within a cirrhotic liver, LT is theoretically the best treatment, removing both the tumour nodules and the underlying liver cirrhosis. However, post-LT survival can be hampered by the risk of tumour recurrence, which can lead rapidly to death [4]. For this reason, LT for HCC must be considered carefully, and preferably offered when there is a reasonable risk of tumour recurrence after LT. Because LT is also an excellent treatment for end-stage liver cirrhosis and because organs from deceased donors are limited, their use should be equitable and fair. An international consensus conference regarding LT for HCC has been recently published [5] and emphasises that each indication must have a comparable result, or if not, must cause no undue prejudice to other recipients with a better prognosis.

Nowadays, the Milan criteria are still used as the benchmark for LT for HCC in cirrhotic patients: they give an overall 5-year survival rate of 65–78% in different studies [6] compared to 70–82% survival for non-tumour indications according to several registries.

We could argue that 5-year overall survival is not a good criterion and that it would be better to consider the individual benefits to the patient, such as the survival gain offered by LT compared to spontaneous survival predicted by prognostic models. According to this suggestion and taking into account survival as predicted by the GRETCH score [7], LT offers a survival benefit of 52% for TNM T1 or T2 tumours, 33% for TNM T3 tumours and 25% for TNM T4A or T4B tumours (unpublished data from a French series of 160 transplant patients). However, deceased organs are scarce and a 5-year overall survival rate of >50% is recommended by the liver-transplant community [8].

The paper of Mergental and co-workers [9] provides interesting data on LT for NC-HCC. This work emphasises the importance of a collaborative database to address questions regarding rare diseases. It provides a large series of data on 105 NC-HCC transplant patients, and shows 5-year overall survival of 49%. For 62 patients, liver transplantation was the primary treatment and 5-year overall survival was 43% (primary-LTs). For the other 43 patients, LT was a rescue treatment for HCC recurrence after primary liver resection (rescue-LTs), and 5-year overall survival was 58%. Pathological data showed more favourable tumour characteristics in the rescue-LTs compared to primary-LTs (pTNM 7th edition, median size of largest tumour, number of patients within the Milan criteria and number of patients with an alpha-fetoprotein level <100 ng/ml). Univariate analysis of factors associated with 5-year survival only identified pathological factors: the number of tumours (≤4 vs. >4), macrovascular invasion and lymph-node involvement. In multivariate analysis, the number of tumours was no longer a factor, and rescue-LT for intrahepatic recurrence within 12 months after partial liver resection was the best predictor for 5-year survival. Five-year overall survival in patients without macrovascular invasion and without lymph-node involvement was 59% and reached up to 83% in the subgroup of rescue-LT patients if LT was performed at >12 months after primary liver resection.
Editorial

The authors acknowledge some limitations to this study because of its retrospective and multicentre design. However, its major limitation is that the European Liver Transplant Registry (ELTR) database was not originally designed to identify the prognostics factors for liver transplantation. Indeed, the best way to address this issue is to study HCC recurrence [10], which is not captured by the ELTR database. Furthermore, pre-LT tumour characteristics (imaging data at listing) should have been recorded to test these variables in an algorithm that could indicate or contra-indicate LT before pathological analysis of the explanted liver.

It is of utmost importance to identify specific criteria associated with lymph-node involvement from pre-operative imaging. For rescue-LT patients, the problem is even more complex because we need to take into account the imaging characteristics before resection, and we can take into account the pathological characteristics of the primary resection before LT indication. Before recommending resection, we need to access data for all patients who have undergone resection to be able to assess the proportion of patients that are no longer eligible for LT at the time of recurrence.

Using the data described in this paper, and in accordance with the international consensus statement, only patients without pathological macrovascular invasion and without lymph-node involvement should be referred for liver transplantation (S5 = 59%). However, these data are analysed after transplantation on the explanted liver and the accuracy of imaging to predict these criteria was not tested in this study. If patients were primarily resected, all patients with recurrence that occurs in >12 months after resection could be referred for LT, whatever the pathological results of the resection and whatever the pathological results of the explanted liver (S5 = 71%). Moreover, according to the multivariate analysis, size and number of tumours are no longer prognostic factors for overall survival after LT for NC-HCC. However, in the largest published study of resected NC-HCC [11], in addition to vascular invasion, tumour size (>5 cm), number of tumours and tumour differentiation were associated with a patient's prognosis. Because of the complexity of this question addressed herein, the relatively small number of patients within this series and the previously mentioned limitations, the conclusions from this study need to be handled with caution. This study mostly underlines the need for prospective studies in the field of liver transplantation for HCC. We need to systematically access the first pre-LT images for tumour characteristics, the response to treatment performed during the waiting period, the kinetics of the tumour during the waiting period (imaging and serological markers), and the rate of drop-out from tumour progression. A lack of this information means no further progress can be made to improve patient selection or to identify new prognostic markers.

Based on this study and previously published studies, it is not possible to recommend primary LT for NC-HCC whatever the number and the size of HCC. Primary resection must be the standard of care for these patients and LT must be offered only for patients with late recurrence after resection or with unresectable HCC but with favourable prognostic factors such as AFP level below 100 ng/ml, less than four tumours, maximum tumour diameter of 5 cm, no vascular invasion and no lymph node involvement assessed on imaging at listing for LT.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References