

The multiple aspects of liver transplantation for hepatocellular carcinoma: comments on the recommendations from the consensus conference

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Abstract: Hepatocellular carcinoma (HCC) is a recognized indication for liver transplantation (LT) as it can at the same time provide a radical oncological resection and prevent its recurrence treating the hepatic disease. However the shortage of donors and the long time on waiting list forces the hepatologists and transplant surgeons to adopt bridging locoregional treatments to prevent the drop out and to perform downstaging treatments to offer a chance of radical intervention to more patients. The therapeutical strategies for patients suffering from HCC are various and different choices should be considered according to each patient's clinical situation according to prognostic and staging systems. Recently recommendations have been published on *Lancet Oncology* about this topic. These guidelines are very helpful in choosing among the different therapeutic options and in the management of patients in waiting list. Here we briefly summarize and comment the main features covered in the recommendations.

Keywords: Barcelona clinic liver cancer classification; hepatocellular carcinoma (HCC); liver cirrhosis; liver transplantation (LT)



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Hepatocellular carcinoma (HCC) is unanimously recognized as a suitable indication to liver transplantation (LT) (1). However the risk of high mortality due to tumor recurrence fuels the debate on what survival threshold to be considered acceptable for transplantability and on what prognostic tools can be useful in this assessment. In this setting the recommendations drafted by the international consensus conference are of paramount importance in driving the clinical practice of transplant surgeons around the world (2).

These recommendations focus on several aspects of the problem: the global assessment of liver transplant candidates, the criteria for listing cirrhotic and non-cirrhotic patients, the role of downstaging, the option of living donor for these transplant candidates and the management of these patients while in waiting list and after the LT.

In the review published on *Lancet Oncology* the following guidelines have been proposed.

The BCLC algorithm is recommended for the choice

of treatment for patients with HCC, after the diagnostic assessment has been concluded with dynamic imaging techniques, without the need for biopsy. The selection of candidates for LT should still observe the Milan criteria (MC); although some studies report that some expansion of these criteria can yield comparable outcome, the level of recommendation for this opportunity is still weak. The microvascular invasion, an important prognostic factor for survival after LT, cannot be considered when listing a candidate for LT because it cannot be reliably detected with the actual diagnostic tools. However the absence of microvascular invasion, together with the absence of lymph node metastasis are essential conditions for salvage transplantation in patients with recurrent HCC after resection.

Procedures of downstaging may be considered when they allow post-LT outcome comparable to transplants performed for patients meeting the criteria without need for

downstaging. LT candidates should be strictly monitored and offered bridging procedures to LT when at risk of dropping out from waiting list. If they progress beyond MC they should be either downstaged if eligible, or definitely excluded.

Living donor LT (LDLT) should be performed in highly specialized centers; in case of graft failure, DDLT (Deceased donor liver transplantation) should be reserved to those patients who underwent LDLT within the regional accepted criteria for DDLT.

After LT the patients should undergo imaging studies for follow up; no specific adjuvant immunosuppressive or antitumoral therapies are recommended. Recurrent HCC can be treated with surgical resection if possible, but LT is not recommended (2).

The recommendations cover the major aspects related to the topic of LT for HCC but some considerations are needed particularly about the management of the patients before LT.

The BCLC system is considered the main staging and prognostic system for patients with HCC, which still guides the decisions of hepatologists and transplant surgeons on which treatment option fits better the patient's condition. The strict therapeutical algorithm of the BCLC system forces to standard treatments, which may not be the best option for every patient.

An example of the lack of accuracy of the BCLC system is the treatment option for cases of intermediate or advanced resectable HCC in patients with preserved liver function. Such patients fall in the BCLC-B or C stage, and according to these algorithm should undergo only palliative strategies, like TACE or sorafenib. A recent multicentric Chinese study reported a marked survival benefit of hepatic resection over transarterial chemoembolization (TACE) for patients with BCLC stage B HCC (3,4). Similar good results for resection of HCC at BCLC-B or C were reported by other hepato-biliary centers as well (5).

Those patients who underwent a radical surgical resection experienced a significantly increased survival especially in the long term (at three and five years), over those who underwent TACE according to the BCLC therapeutical algorithm.

This report may contribute to change the attitude towards the treatment of HCC. Although an easy algorithm is an essential basis, the best therapeutical option should derive from a new enriched system, which considers the complexity of each clinical case from both a surgical and medical perspective.

The shortage of organs is dramatically affecting the life expectancy of the cirrhotic population, decreasing their survival on waiting list. This condition pushes the main hepato-biliary surgical centers to expand the pool of candidates to hepatic surgery, in order to save organs for severely cirrhotic patients and for those who experience tumor recurrence after hepatic resection.

This observation supports the importance of choosing the optimal pre-LT strategy according to the regional variables related to the extended time in waiting list due to the limited availability of donors and the gravity of the other candidates. In this outlook, locoregional treatments as bridge to LT may be crucial in some centers where the risk of disease progression is increased due to the long waiting list.

The Danish model is a precious tool, which focuses the attention of an expert scientific community on specific topics, and assesses neutrally the validity of the evidences supporting the considered recommendations, thanks to the judgment of an external commission. The evidence-based medicine can be very helpful in the approach to some multidisciplinary issue, and the indication to LT for HCC is one of these situations. For instance these recommendations indicate that lesions less than 1 cm should not be accounted as tumors; this consideration can totally overturn the therapeutical strategy adopted by many centers in the pre-LT management.

However we should bear in mind that some technical development and therapeutical progresses have been pursued without the validation from literature-derived evidences, especially at the birth of hepato-biliary surgery and in the field of transplantation. An example is the technique of the piggy-back cava vein preparation, which has been immediately adopted by the majority of transplantation center although literature evidences have never confirmed the superior outcome of this technique over the conventional total caval clamping with extracorporeal bypass.

In conclusion these recommendations are a useful instrument to guide physicians in the clinical practice and to promote the adoption of a uniform strategy among the transplant centers.

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