Published in final edited form as:

Clin Res Hepatol Gastroenterol. 2012 August ; 36(4): 316–318. doi:10.1016/j.clinre.2012.04.006.

Liver transplantation for hepatocellular carcinoma: time for an international consensus

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Summary

Liver transplantation for hepatocellular carcinoma is widely accepted as the best treatment for this cancer. Since transplantation has become widely available (mid-1980s), there has been no international consensus for this specific setting. This has now been done, and takes into account regional differences (cadaveric and living donor) and introduces expanded criteria, which vary according to the dynamics of the regional waiting list.

Hepatocellular carcinoma (HCC) is a major health problem worldwide¹, which continues to increase because of viral hepatitis B and C epidemics but also because of alcoholic and non-alcoholic liver disease². Liver transplantation (LT) is theoretically the best treatment for HCC because it removes known tumours, unknown tumours and underlying liver cirrhosis. However, this treatment is limited by the risk of tumour recurrence, which can rapidly lead to patient death³. Indications for a LT for HCC must thus be considered carefully before offering it to patients who have 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 nationally, their use should be equitable and fair.

To review the current practice regarding LT for HCC and to develop internationally accepted statements and guidelines, an international consensus conference was held in December 2010, in Zurich (Switzerland). Nineteen expert working groups prepared evidence-based reviews and drafts that answered 19 specific questions. An independent jury of nine members reviewed the submissions and made 37 final recommendations after debating with experts. Their findings were published in *Lancet Oncology*⁴ (summarized in Figure 1).

The first group of recommendations (1st–6th) assessed candidates with HCC on liver cirrhosis for a LT. For HCC diagnosis, non-invasive criteria based on a dynamic CT or MRI was reinforced for lesions >1 cm (tumour biopsy not recommended). It was recommended that lesions <1 cm diameter should not be taken into account when making a decision either for or against transplantation.

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For the treatment-option choice, the BCLC staging system was endorsed. The recommendation to use the TNM system (7th edition) for pathological-examination staging was surprising because this classification was never validated in the transplant setting but only in liver resection.

The second group of recommendations referred to criteria that listed candidates with HCC in cirrhotic livers due to receive a deceased donor-liver transplantation (DDLT) (7th–14th). In order to warrant equality on the waiting list, LT for HCC must have a predicted 5-year survival comparable to non-HCC patients. The benchmark criteria are Milan criteria (one HCC ≤ 5 cm or ≤ 3 HCC ≤ 3 cm without macrovascular invasion or extrahepatic spread). Nonetheless, new prognostic markers should be found in addition to the number and size of detected HCCs. The prognostic value of α-fetoprotein levels are noted but no cut-off value can be recommended. The door is also open for a modest expansion of criteria to take into account the dynamics of the waiting list for these expanded criteria, considering that a worse prognosis could be tolerated if there is no undue prejudice for patients without HCC.

The third group of recommendations concerns transplantation for HCC candidates with a non-cirrhotic liver (15th–6th). Here the jury noted that the Milan criteria are not applicable and large tumours are eligible for liver transplantation without decreasing patient prognosis.

The fourth group of recommendations focused on the role of down-staging (17th–21st) and considered that a LT could be proposed for down-staged patients without a clear limit, but noted that the prognosis of these patients should be the same as those for non-down-staged patients at the same tumour stage. No recommendation could be made for preferring a specific loco-regional therapy.

The fifth group of recommendations considered the management of patients on a waiting list (22nd–27th). They recommended periodic monitoring of patients with imaging and α-fetoprotein measurements. Treatment was only recommended for patients with one HCC ≤ 5 cm or two or three HCCs each of ≤ 3 cm (T2), plus an expected waiting time of >6 months. Patients progressing beyond these criteria must be placed on hold and considered for down-staging: patients who will be ineffectually treated should be removed from the waiting list.

The sixth group of recommendations focused on the role of living donor-liver transplantation (LDLT) (28th–31st). The jury kept an open door on this controversial topic, accepting LDLT if the expected 5-year survival was similar to comparably staged patients receiving DDLT. Nonetheless, in cases of graft failure after LDLT, re-transplantation from a cadaveric organ was only recommended if the patient was transplanted within the accepted regional criteria.

Finally, the seventh group of recommendations referred to post-transplant management (32nd–37th). Monitoring at 6–12 months, with dynamic imaging and α-fetoprotein measurement, was recommended, but nothing specific was said concerning the choice of immunosuppressive therapy. Tumour recurrence should be appropriately treated from resection to systemic therapy, but without re-transplantation.

The most surprising conclusion from this consensus was that experts did not discuss an alternative treatment for small HCC (UNOS T1) that has developed in well-compensated cirrhosis and is curable by surgery or radiofrequency ablation. Many studies have shown that these treatments can be used as first-line therapies, with liver transplantation reserved for any recurrence. This treatment policy, with very strict surveillance, would offer salvage transplantation in the majority of patients⁵. This leads to significant graft economy for patients who will not experience tumour recurrence or who will develop a LT contra-indication before recurrence. In addition, the experts did not discuss patients who achieve a

complete respond during the waiting time and who have no more LT indication. In fact, is it ethical to expose these patients to the LT procedure risk?

In conclusion, the major conclusions made by this international consensus conference underlined already existing benchmarks but also introduced flexibility into the recommendations, allowing regional adaptation according to the dynamics of the waiting list.

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Figure 1.

Graphical summary of final recommendations as published in Lancet Oncology