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Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report

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Abstract

Although liver transplantation is a widely accepted treatment for hepatocellular carcinoma (HCC), much controversy remains and there is no generally accepted set of guidelines. An international consensus conference was held on Dec 2–4, 2010, in Zurich, Switzerland, with the aim of reviewing current practice regarding liver transplantation in patients with HCC and to develop internationally accepted statements and guidelines. The format of the conference was based on the Danish model. 19 working groups of experts prepared evidence-based reviews according to the Oxford classification, and drafted recommendations answering 19 specific questions. An independent jury of nine members was appointed to review these submissions and make final recommendations, after debates with the experts and audience at the conference. This report presents the final 37 statements and recommendations, covering assessment of candidates for liver transplantation, criteria for listing in cirrhotic and non-cirrhotic patients, role of tumour downstaging, management of patients on the waiting list, role of living donation, and post-transplant management.

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P-AC and ML contributed equally to this work.

Contributors
P-AC and ML contributed to conference organisation and collection and analysis of data. PMMB contributed to the methods of the consensus conference and writing of recommendations. GJG contributed to conference organisation. AP and BL wrote recommendations. All authors wrote the manuscript.

Conflicts of interest
The authors declared no conflicts of interest.

Introduction

Although liver transplantation was first done in human beings by Tom Starzl in 1963, the procedure did not begin to gain wide acceptance until the mid-1980s, when effective immunosuppression with ciclosporin became available. Currently, overall 1-year and 5-year survival after liver transplantation exceeds 85% and 70%, respectively, in most centres.[1,2]

Hepatocellular carcinoma (HCC) is a major health problem worldwide, which continues to increase because of the association of HCC with hepatitis B and C viruses. HCC was one of the first indications for liver transplantation, because it was postulated that this approach would eliminate the tumour and cure the underlying liver disease. However, it soon became apparent that the success of liver transplantation depends on the tumour load; patients with extensive disease had very poor outcomes, whereas most patients with small tumours could be cured. This led to many controversies around the use of liver transplantation in patients with HCC, such as the selection of patients in the context of worldwide organ shortage, control of the tumour load while patients wait for a graft, use of living donors, and the choice of immunosuppression or adjuvant therapies.

The goal of liver transplantation, regardless of the underlying disease, is providing liver recipients with the maximum benefit possible from the limited resource of deceased and living donor organs, in a fair, ethical, and cost-effective manner. Thus, indications for the procedure and allocation of donor organs are closely scrutinised by all stakeholders in liver transplantation. With the endorsement of most international societies concerned with liver transplantation or HCC, we organised a conference that aimed to reach wide consensus throughout the medical and non-medical population on various aspects of the use of liver transplantation for patients with HCC, based on the best available evidence.

Methods

An international consensus conference on liver transplantation for HCC was held on Dec 2–4, 2010, in Zurich, Switzerland, under the auspices of ten international societies focused on liver diseases or transplantation, with the aim of establishing a consensus regarding indications for liver transplantation in patients with HCC and to provide internationally accepted statements and guidelines for the conduct of liver transplantation programmes. For this purpose, we developed a novel format based on the Danish model (figure).[3] The organising committee identified key topics and appointed 19 working groups composed of four to six experts from various areas of medicine, selected on the basis of their scientific and clinical records, to prepare reviews of the evidence and draft recommendations. Working groups were asked to follow the Oxford classification of levels of evidence.[4] The material prepared by the various panels is available as a supplement of *Liver Transplantation*.[5–24] Each working group did an English language literature search of Pubmed, Embase, and Scopus databases, and the Cochrane central register of controlled trials. Text, keywords, and medical subject heading terms were used for titles and abstracts. Manual cross-referencing was also used to find further relevant articles. Search terms and dates varied according to topic (webappendix). A jury of nine members, who were selected from various clinical and academic areas and who were not actively involved in liver transplantation, was appointed to review and comment on the submitted papers and to finalise and grade the final recommendations.

Around 300 participants from five continents attended the meeting in Zurich. Each of the 19 working groups, assisted by members of the jury, prepared statements associated with a level of evidence from their review of the literature. The chair of each working group gave a 15-min presentation covering specific questions, followed by questions from the jury and the

audience. The prepared statements could be modified in real time according to the debates during the conference. Then, a poll of the audience was obtained through an anonymous electronic voting system to inform the jury of the strength of consensus.

The jury met independently after the conference to produce the final recommendations, based on the expert reports, debates, and attendee voting. The jury concluded by voting to assign a level of evidence for each recommendation, according to the Oxford classification, with respect to diagnosis, prognosis, or therapy. They also determined the strength of each recommendation according to the grading of recommendations assessment, development, and evaluation system (GRADE).[25] From the initial statements and recommendations proposed by the panels of experts, 27 were dropped or merged with other statements or recommendations, ten were left unchanged, and another 27 were reworded. Among the definitive 37 statements and recommendations, the level of evidence proposed by the experts was modified in three cases by the jury after discussion with the statistician (PMMB).

The present review was prepared by a writing committee, which included the president (AP), vice president (BL), and statistician (PMMB) of the jury, along with three members of the organising committee (ML, GJG, P-AC). The manuscript was circulated among the working groups for confirmation of accuracy of the data with no possibility to alter the recommendations. The final version was approved by each member of the jury. The recommendations are presented in table 1.

Assessment of candidates with HCC for liver transplantation

The purpose of cancer staging is to accurately predict prognosis and to link tumour stage with specific therapeutic interventions. The ideal staging system for HCC should take into account tumour stage, liver function, and functional status of the patient. Several staging systems have been developed over the past three decades, although none has gained worldwide acceptance (table 2).[26–34] The Barcelona Clinic Liver Cancer (BCLC) and Cancer of the Liver Italian Program (CLIP) staging systems have been the most popular in Europe and the USA, and the Japan Integrated Staging Score (JIS) in Japan. The BCLC is the only system that links prognosis with treatment recommendations, and thereby was selected in several major trials of HCC therapy. For example, the role of portal hypertension in selecting patients for major liver resection versus liver transplantation has been validated in Japan[35] and the USA.[36]

Pathological features in the explanted liver that have prognostic value for staging HCC include tumour size and number of nodules, satellite lesions, vascular invasion (macroscopic or microscopic), and lymph-node metastases. However, staging systems to guide therapy before liver transplantation are necessary and are mainly based on imaging information. Preoperative and post-transplant liver staging systems can be used in assessing outcome. This led to recommendations 1 and 2: (1) when considering treatment options for patients with HCC, the BCLC staging system is the preferred staging system to assess the prognosis of patients with HCC; (2) the TNM system (7th edn), including pathological examination of the liver, should be used for determining the prognosis after transplantation with the addition of the assessment of microvascular invasion.

Despite incremental technological advances in cross-sectional imaging techniques (ultrasonography, CT, and MRI), standard imaging methods can underestimate or overestimate the extent of HCC in up to 25% of cases, compared with pathological findings of the explanted liver.[18] Recent reports suggest that either dynamic CT or MRI, including unenhanced, arterial, portal venous, and delayed phases, provide improved sensitivity and specificity compared with standard techniques of the past. Currently, there is no data showing the superiority of either MRI or CT. Conclusive imaging features rely on the

presence of arterial enhancement followed by washout on portal venous or delayed imaging.[37] Such examinations should follow established protocols, which define the amount and rate of contrast given, the precise individualised timing of image acquisition, and image reconstruction with minimum slice thickness. Dynamic ultrasonography has improved the accuracy of ultra sonography, but is less useful than CT or MRI because of the inability to reliably acquire images of the entire liver during a particular contrast phase. Bone scintigraphy has been used for evaluating bone metastases; however, the technique is poor in terms of cost-effectiveness when used routinely. There is insufficient data to propose ^{18}F-fluorodeoxyglucose (FDG)-PET for staging HCC before liver transplantation. These finding are summarised in recommendations 3 and 4: (3) either dynamic CT or dynamic MRI with the presence of arterial enhancement followed by washout on portal venous or delayed imaging is the best non-invasive test to make a diagnosis in cirrhotic patients suspected of having HCC and for preoperative staging; (4) extrahepatic staging should include CT of the chest, and CT or MRI of the abdomen and pelvis.

Because of improvements in the accuracy of non-invasive imaging, the need for liver biopsy in the work-up of cirrhotic patients with HCC being considered for liver transplantation has changed in recent years. The specificity of liver biopsy is close to 100%, but sensitivity varies depending on location of the tumour, needle size (86–90% with an 18 gauge cutting needle, 67% with 21–22 gauge needle), and tumour size (>90% for nodules >1 cm *vs* 83% for nodules <1 cm). A positive tumour biopsy is clinically relevant to rule in a diagnosis of HCC, but a negative biopsy is less useful. There is also the risk of tumour seeding after liver biopsy, which has been reported to be 2·7% (95% CI 1·8–4·0) with a median time interval between biopsy and seeding of 17 months (IQR 7–48).[38]

The American Association for the Study of Liver Disease (AASLD) has proposed an algorithm for diagnosis of HCC based on availability of state-of-the-art CT or MRI.[39] These data are summarised as recommendations 5 and 6: (5) tumour biopsy is not required in cirrhotic patients considered for liver transplantation who have high-quality dynamic CT or MRI findings typical for HCC and a lesion larger than 1 cm according to current AASLD guidelines; (6) for patients with lesions smaller or equal to 10 mm or atypical findings, non-invasive imaging does not allow an accurate diagnosis, and should not be used to make a decision for or against transplantation.

Criteria for listing candidates with HCC in cirrhotic livers for deceased-donor liver transplantation

In the context of shortage of available grafts, decisions have to take into account the collective benefit of all potential liver recipients, in addition to the benefit for the individual patient. Liver transplantation achieves excellent results in patients with limited tumour load. Patients with solitary HCC of less than 5 cm or with up to three nodules of less than 3 cm (the Milan criteria[40]) have a 5-year survival of 70% after liver transplantation, with recurrence in less than 10%. This survival matches post-transplant survival of most other indications for liver transplantation.[1,2]

In the context of organ shortage for liver transplantation, an extension of the boundaries of transplantation for HCC must take into account the benefit for individual HCC patients as well as the consequences for all potential liver recipients. Whether, and to what extent, post-transplant survival could be lowered, because of expansion of the HCC receiver pool, while remaining acceptable, depends on the effect on mortality for non-HCC patients awaiting transplantation. Even though a survival opportunity considerably lower than that achieved in non-HCC patients might be considered worth the risk of surgery for some patients with HCC, the negative effects on others on the donor list must be taken into consideration. This

led to recommendation 7: liver transplantation should be reserved for HCC patients who have a predicted 5-year survival comparable to non-HCC patients.

Among criteria used for listing patients with HCC, gross features of tumours are important. Burroughs and colleagues[41] did a meta-analysis of 101 studies assessing the effect of HCC staging in terms of size and number of nodules on post-transplant recurrence and survival. 74 of the studies, comprising 22 432 patients, were used for quantitative analysis. There was variability in the reporting of tumour characteristics, with information missing for time on the waiting list, immunosuppression, and bridging therapy. Two-thirds of the studies were based on explant findings, and few compared pretransplant imaging with explant data. If multiple versus single nodules were considered, the definition of multiple was poorly reported. Burroughs and colleagues[41] concluded that assessment of the diameter of the largest nodule or total diameter of nodules was the best predictor of outcome, and that total tumour size (sum of diameters) of 10 cm or larger (*vs* <10 cm) was associated with a four-times increased risk of death or recurrence. Measurement of volume might be a better way to assess tumour burden, but the data to support this are not yet available.[42] A study using the Organ Procurement and Transplant Network (OPTN) database suggested that a total tumour volume cutoff at 115 cm^3 and α-fetoprotein concentration higher than 400 ng/mL could discriminate between patients with acceptable outcome and those with poor outcome.[43] There is insufficient evidence regarding the effect of number of nodules on outcome of liver transplantation.

This led to recommendation 8: preoperative assessment of the size of the largest tumour or total diameter of tumours should be the main consideration in selecting HCC patients for liver transplantation. In 1996, after a period of unrestricted indications for liver transplantation, associated with overall 5-year survival below 50%, the Milan criteria were introduced. These criteria set restrictive limits for size and number of tumours in candidates for liver transplantation.[40] Mazzaferro and colleagues[44] did a systematic review that included 90 studies, comprising 17 780 patients over 15 years (1612 patients in level 1b studies, 16 043 in level 2 studies, and 125 in level 4 studies). Their review showed that the Milan criteria are an independent prognostic factor for outcome after liver transplantation. Application of the Milan criteria for patients with HCC with chronic hepatitis and cirrhosis achieves similar post-transplant survival to that in non-HCC indications. In the European Liver Transplant Registry (ELTR), Organ Procurement and Transplantation Network (OPTN), and Australia and New Zealand Liver Transplant Registry (ANZLTR), 5-year survival for non-HCC was 65–87%.[1,2,45] The jury concluded with recommendation 9: the Milan criteria are currently the benchmark for selection of HCC patients for liver transplantation, and the basis for comparison with other suggested criteria.

As evidence accumulated of good outcomes in some patients outside the Milan criteria, there was a drive to identify expanded criteria and to increase the number of eligible candidates for liver transplantation. Among the many proposals, only the University of California San Francisco (UCSF) criteria (one tumour ≤6·5 cm, three nodules at most with the largest ≤4·5 cm, and total tumour diameter ≤8 cm) have been prospectively validated by the proponent group, with outcome data comparable to those from other retrospective studies.[46,47] This is summarised in recommendation 10: a modest expansion of the number of potential candidates may be considered on the basis of several studies showing comparable survival for patients outside the Milan criteria.

It is essential to consider how expansion of criteria beyond the Milan criteria might affect the survival of candidates for liver transplantation who do not have HCC. According to studies based on Markov models[48] using data from the USA, patients outside the Milan criteria would need to achieve 5-year survival of 60% or higher to prevent a substantial

decrement to the life-years available to the entire population of candidates for liver transplantation. The effect on non-HCC patients could vary widely, depending on the composition of the population on the waiting list and the scarcity of available donor livers in a transplant region and in individual centres. Any decision by a centre to expand criteria should take into account the current mortality on the waiting list, and should only be done if a low mortality will not be substantially increased by additional expanded-criteria cases. For example, a centre with very low or no mortality on the waiting list might expand their criteria for patients with HCC with lower post-transplant survival than that expected for non-HCC candidates, whereas such strategy would not be acceptable in another centre with a high death rate on the waiting list. Thus, the jury proposed recommendation 11: patients with a worse prognosis may be considered for liver transplantation outside the Milan criteria if the dynamics on the waiting list allow it without undue prejudice to other recipients with a better prognosis.

Since gross features of tumours are unable to define subclasses of patients with better biology and outcome, several biomarkers have been studied—eg, G3, EpCAM, miR26, and poor-survival gene signatures. However, these biomarkers have not been studied in the setting of liver transplantation.[49] Several studies highlighted the value of preoperative α-fetoprotein concentrations in predicting outcome after liver transplantation,[43,50,51] but there is no agreement on the cutoff values to consider, which ranged from 200 to 1000 ng/mL. A recent study using the Scientific Registry of Transplant Recipients (SRTR) data suggested adding α-fetoprotein concentration to total tumour volume as a predictor of outcome after liver transplantation.[43] In several studies, α-fetoprotein concentration lower than 400 ng/mL has been used in selecting patients for liver transplantation after downstaging protocols, in addition to criteria based on tumour size and number.[52] Another group found that dynamic changes in α-fetoprotein concentrations higher than 15 ng/mL are the most relevant preoperative predictor of recurrence and overall survival after orthotopic liver transplantation.[50] Recommendations 12 and 13 summarise this topic: (12) α-fetoprotein concentrations add prognostic information in HCC patients and may be used for making decisions regarding transplantation in combination with imaging criteria; (13) biomarkers other than α-fetoprotein cannot yet be used for clinical decision making regarding liver transplantation for HCC.

HCC often involves branches of portal or hepatic veins (or both), causing a tumour thrombus. Vascular invasion of HCC affects prognosis after liver transplantation.[53–55] Macrovascular invasion involves branches of portal or hepatic veins, or both. It can be detected using high-quality imaging and in a pathological specimen, and is generally considered an absolute contraindication for liver transplantation. Micro vascular invasion, which is identified only by microscopic observation, is associated with poorer outcome or increased recurrence rates after liver transplantation. Although it correlates with larger tumour size (>3 cm), multiple nodules, histological grade (moderately *vs* poor differentiated), and gross features such as confluent multinodular type,[56] microvascular invasion cannot be reliably detected before transplantation and is therefore not useful for clinical decision making.

Conventional imaging modalities are ineffective for preoperative detection of microvascular invasion. Only one study suggested a value for PET in predicting microvascular invasion.[57] Several studies from Japan suggested that serum concentrations of des-gamma-carboxyprothrombin (also known as protein induced by vitamin K absence [PIVKA]) correlate well with microvascular invasion.[58,59] Positive and negative correlations of α-fetoprotein with microvascular invasion have been reported. The available data led to recommendation 14: indication for liver trans plantation in HCC should not rely on microvascular invasion because it cannot be reliably detected prior to transplantation.

Criteria for HCC candidates with non-cirrhotic livers

Although most HCC occurs in patients with liver cirrhosis, about 10% of cases arise in absence of cirrhosis. In such patients, diagnosis is often made at an advanced stage. Resection is currently the preferred therapeutic option, when feasible, since patients with good liver reserve have high tolerance for extensive liver resection.[60] However, as in cirrhotic patients, the risk of local recurrence is high, ranging from 30 to 73%, and affects 5-year overall survival (25–81%) and disease-free survival (24–54%).[61,62] Several pathological features are associated with poor prognosis, such as the presence of satellite or multiple nodules, microvascular and macrovascular invasion, and R1 resection. The subtype of fibrolamellar HCC seems to have similar outcomes.[63]

Data from the ELTR suggest that liver transplantation might be appropriate in some non-cirrhotic patients with recurrent HCC after resection, with long-term survival approaching 60% at 5 years.[64] In this study, the absence of cirrhosis or fibrosis, and seronegativity for hepatitis C and hepatitis B virus was confirmed in all patients. Macrovascular and lymph-node invasion, and early recurrence (<1 year) after resection were significant risk factors for poor outcome. Tumour diameter and Milan criteria of the initial HCC were unrelated to outcome.

There are few reports of cases of primary liver transplantation in non-cirrhotic patients with HCC.[64,65] The data available suggest that the risk factors for poor outcomes after liver transplantation are the same as those identified for recurrent disease after resection. Patients without these risk factors had a 5-year survival of 67%, even though most had tumours outside the Milan criteria. This information led to recommendations 15 and 16: (15) the Milan criteria and its modifications are not applicable to patients with HCC developing in a non-cirrhotic liver. Such patients with non-resectable HCC and absence of macrovascular invasion and extrahepatic spread may be considered as appropriate candidates for liver transplantation; (16) patients with HCC in a non-cirrhotic liver, who were treated by resection and have intrahepatic recurrence of HCC and no evidence of macrovascular invasion or extrahepatic spread, may be considered for salvage transplantation.

Role of downstaging of HCC

The goal of downstaging using locoregional therapy—eg, alcohol injection, radiofrequency ablation (RFA), transarterial chemoembolisation (TACE), transarterial radioembolisation (TARE), or liver resection—is to decrease the tumour size and number in patients initially presenting with tumours that do not meet locally acceptable criteria for liver transplantation.

Success in downstaging has been reported in many studies, although most of these are uncontrolled observational studies with no method emerging as superior and each carrying some risk. The largest experience is with TACE and RFA.[66] Two prospective studies showed that survival after liver transplantation in patients with large tumour burden successfully treated by downstaging was similar to survival in patients who initially met the criteria for transplantation.[52,67] These issues are addressed in recommendations 17 and 18: (17) transplantation may be considered after successful downstaging; (18) liver transplantation after successful downstaging should achieve a 5-year survival comparable to that of HCC patients who meet the criteria for liver transplantation without requiring downstaging.

There is debate about how best to assess successful downstaging. European Association for the Study of the Liver (EASL) guidelines suggest that such assessment should be exclusively based on the amount of viable tumour, as differentiated from necrosis by contrast CT or MRI.[68] Most available reports have used the Milan criteria to define

successful downstaging.[52,67,69] There is currently no well defined upper limit for size and number of lesions as eligibility criteria for downstaging, although the presence of vascular invasion and extrahepatic disease are generally considered absolute con train dications. Some groups add serum α-fetoprotein concentrations for assessment of downstaging; however, there is no agreement on a threshold. Recommendations 19 and 20 address downstaging: (19) criteria for successful downstaging should include tumour size and number of viable tumours; (20) α-fetoprotein concentrations before and after downstaging may add additional information.

Once a tumour has been successfully downstaged to within acceptable criteria, a minimum observation period of 3 months is often recommended before considering liver transplantation. It is crucial to define criteria for failure of downstaging, which may include, before listing: failure to achieve listing criteria, tumour progression with development of vascular invasion, extrahepatic spread, or tumour size and number remaining beyond inclusion criteria; and, after listing: tumour progression requiring delisting and recurrence of HCC after liver transplantation. This consideration led to statement 21: based on existing evidence, no recommendation can be made for preferring a specific locoregional therapy for downstaging over others.

Managing patients on the waiting list

With increases in waiting times for liver transplantation in many centres, it has become common practice to monitor patients with HCC to ensure that they remain within the acceptability criteria for liver transplantation. Strategies have also been developed to treat patients whose HCC is at risk or shows signs of progression while waiting for a graft. There is no agreement about specific timing or optimum imaging methods to use for these patients, although a 3-month interval is common.

Recommendations are based on the known capabilities of the imaging methods used for diagnosis and staging of HCC (see recommendations 3 and 12). There are also reports showing that a rise in α-fetoprotein concentration is associated with poorer outcome after liver transplantation, and of reduction in that risk by successful locoregional therapy. This information is reflected in recommendation 22: periodic waiting-list monitoring should be performed by imaging (dynamic CT, dynamic MRI, or contrast-enhanced ultrasonography) and serum α-fetoprotein measurements.

Dropout of HCC patients on the waiting list is common because of cancer progression or other medical reasons. Locoregional therapy as a bridging strategy for patients on the waiting list aims to decrease tumour-related dropout rates and reduce the incidence of recurrent diseases after liver transplantation. Several cohort studies and a preliminary analysis of large registries suggest that bridging strategies with locoregional therapy are likely to be beneficial for patients having to wait 6 months or longer.[70] There is, however, no evidence that bridging strategies are of any benefit in patients with United Network for Organ Sharing (UNOS) T1 tumours (<2 cm). Bridging strategies might be appropriate for patients with UNOS T2 lesions (one nodule 2–5 cm or three or fewer nodules each ≤3 cm) who are likely to wait 6 months or longer. The presence of larger tumours and high α-fetoprotein concentrations seem to predict a higher risk for dropout.

Although the most popular bridging strategy is TACE, pathological studies show a marginal advantage for RFA in terms of tumour necrosis.[71,72] Liver resection before transplantation in patients with well preserved liver function, and newer strategies such as a combination of TACE with RFA and use of ^{90}yttrium radioembolisation or targeted therapies, have shown some benefits in preliminary studies. This topic is summarised by the following three statements from the jury: (23) based on current absence of evidence, no recommendation

can be made on bridging therapy in patients with UNOS T1 (≤2 cm) HCC; (24) in patients with UNOS T2 (one nodule 2–5 cm or three or fewer nodules each ≤3 cm) HCC (Milan criteria) and a likely waiting time of longer than 6 months, locoregional therapy may be appropriate; (25) no recommendation can be made for preferring one type of locoregional therapy to others. The topic also generated two additional recommendations: (26) patients found to have progressed beyond criteria acceptable for listing for liver transplantation should be placed on hold and considered for downstaging; (27) patients with progressive disease, in whom locoregional therapy intervention is not considered appropriate or is ineffective, should be removed from the waiting list.

Role of living-donor liver transplantation for HCC

Living-donor liver transplantation (LDLT) using the right or left hemiliver of a healthy donor is the only option for liver transplantation in some countries, particularly in Asia, where there is limited or no availability of deceased-donor organs. LDLT has also been used in other countries with well established programmes for organ donation from brain dead or non-heart-beating donors, because of organ shortage, long waiting times associated with deaths on the waiting list, drop-out due to medical reasons, or progression of tumours beyond acceptable criteria.

The main issue in LDLT is donor safety, because of the risk of complications or death, even if small. The concept of double equipoise was proposed to describe the balance between the recipient's survival benefit with LDLT and the risk of a complication or death of a healthy donor.[73] The risks and benefits need to be openly discussed and understood by all parties involved in such cases, and meet the test of equipoise.

Some studies have suggested a higher risk of tumour recurrence with the use of partial grafts from living relatives versus whole grafts from deceased donors. Six studies compared deceased-donor liver transplantation (DDLT) and LDLT for HCC, including a report from a multicentre US consortium of LDLT centres.[74–79] No convincing difference in outcome could be identified according to type of graft, although a higher risk of recurrence was noted in fast-tracked patients, since a short delay between diagnosis and liver transplantation might not allow enough time for the biological behaviour of the tumour to manifest. Therefore, it might be important to consider a period of observation (eg, 3 months) when offering LDLT in recipients with HCC. This topic is covered in recommendations 28 and 29: (28) LDLT is acceptable for HCC patients who have an expected 5-year survival similar to comparably staged patients receiving a deceased-donor liver. In LDLT, careful attention should be given to psychosocial considerations regarding both donor and recipient; (29) LDLT must be restricted to centres of excellence in liver surgery and liver transplantation to minimise donor risk and maximise recipient outcome.

Should LDLT be offered to patients with tumour stages beyond the accepted criteria for listing for deceased donation? This might seem to be ethically acceptable, since unlike deceased-donor donation, other listed patients are not adversely affected by this process. However, the question raises ethical concerns regarding the double equipoise principle, since the risk to the donor might not be acceptable below a certain expected survival threshold for the recipient. There was considerable disagreement among the experts at the conference on what that threshold might be. Those who set a priority on donor protection would not consider offering LDLT to patients with a tumour beyond criteria for DDLT, whereas others supported the procedure even for patients with a very dismal prognosis, to maximise individual patient benefit and patients' choice.

The jury recognised that there are differences in current practice and suggested that any institution using LDLT should take a clear position, make it known to the public, and, when

endorsing criteria beyond those accepted for deceased donation, provide rigorous safeguards to guarantee full disclosure to donor and recipients and to prevent donor coercion and increased risk-taking by the surgical team.

The use of deceased-donor organs is usually justified for graft failure after LDLT.[80] The panel of experts supported use of deceased-donor graft for failed LDLT, even if extended criteria were used. Rates of retrans plantation because of graft failure after LDLT are typically low, and when needed, outcomes are excellent. The jury agreed with the use of retransplantation in recipients who received a living graft within the accepted criteria for liver transplantation. However, based on utility, justice, and equity, they did not support retransplantation for patients who were beyond these criteria, because these patients would not have qualified for DDLT in the first place, and their acceptance of LDLT did not benefit patients on the DDLT waiting list. The vote of the audience at the conference was in line with this re com mendation (46% strongly disagreed and 25% disagreed with the use of retransplantation in patients beyond the accepted criteria). This discussion led the jury to formulate recommendations 30 and 31: (30) in patients following LDLT for HCC within the accepted regional criteria for DDLT, retransplantation for graft failure is justified; (31) in patients following LDLT for HCC outside the accepted regional criteria for DDLT, retransplantation for graft failure using a deceased-donor organ is not recommended.

Post-transplant management

The main concern after liver transplantation for HCC is the risk of tumour recurrence, which occurs in 8–20% of recipients.[81] HCC recurrence is usually seen within the first 2 years after liver transplantation, and is associated with a median survival of less than 1 year (IQR 7–18 months) from the time of diagnosis.[82] The adoption of routine imaging and α-fetoprotein monitoring has led to the detection of early recurrence, with a possibility of cure with ablation therapies in up to a third of cases.[83] However, studies addressing the issue of protocols for monitoring are scarce. A limitation for the use of routine imaging examination (CT or MRI) is the high cost or poor cost-effectiveness to detect HCC recurrence, and most centres have limited their application to every 6 months or yearly intervals for the first 3–5 years after liver transplantation or in the presence of abnormal α-fetoprotein concentrations, leading to recommendation 32: post-transplant monitoring may include 6–12-monthly contrast-enhanced CT or MRI imaging and α-fetoprotein measurements.

There is debate about how to adjust the immunosuppression in HCC patients after liver transplantation. Immunosuppressive drugs are associated with oncogenic properties in experimental models, and most programmes are careful to balance the inherent risks of rejection and tumour recurrence.[84] However, there are no randomised controlled trials (RCTs) that have shown that lowering immunosuppression reduces the risk of HCC recurrence after liver transplantation.

One class of immunosuppressive drugs, the mTOR inhibitors, might be of particular relevance for patients with HCC who receive a liver transplantation, since experimental studies have shown that this drug has strong immunosuppressive effects with concomitant anti-neoplastic properties.[85] Uncontrolled pilot trials and retrospective analyses have suggested that sirolimus, an mTOR inhibitor, was associated with lower tumour recurrence and improved survival after liver transplantation;[86–88] however, these results have not been confirmed in an RCT. This topic is covered in statements 33 and 34: (33) there is currently insufficient evidence from clinical trials to base a recommendation for choosing the type or dose of immunosuppression therapy to influence the incidence of HCC recurrence or its prognosis; (34) based on current evidence, no recommendation can be made on the use of mTOR inhibitors to reduce the risk of HCC recurrence outside clinical trials.

To assess whether adjuvant therapies are effective to decrease post-transplantation tumour recurrence and improve overall survival, the experts identified eight uncontrolled studies (226 patients)[89–96] and four RCTs (213 patients).[96–100] Difficulties in interpreting these studies include variability in the drugs tested (doxorubicin, cisplatin, fluorouracil, gemcitabine, or mithoxanthrone) and in the inclusion criteria and endpoints selected, and small sample sizes. Single-arm, retrospective studies suggest a benefit for using adjuvant therapy, but their level of evidence is too low (level 4) to support recommendations. Controlled studies have also provided inconsistent results.

Two compounds show some early promise: sorafenib and licartin. Sorafenib, a multitargeted tyrosine-kinase inhibitor, has been shown to have an antitumour effect in patients with advanced HCC,[101] and is currently being studied as adjuvant therapy after resection or ablation of HCC in a multicentre phase 3 trial (STORM trial). Licartin, a ^{131}I-radiolabelled murine monoclonal antibody that specifically binds HCC cells, was shown to have a positive effect on prevention of tumour recurrence and on survival, in a small, placebo-controlled, randomised, double-blind study.[97] This led to recommendation 35: current evidence does not justify the routine use of adjuvant antitumour therapy after liver transplantation for HCC outside of a controlled clinical trial.

There is considerable debate about how to treat HCC recurrence after liver transplantation. Most recurrences are associated with systemic tumour dissemination, thus retransplantation is not indicated. A distinction must be made for de-novo HCC, which typically occurs at a later stage and most often in the setting of recurrent hepatitis C and advancing fibrosis. Such cases should probably be treated as having new tumours and retransplantation might be justified;[102] however, the data to support this approach are limited.

Locoregional therapy for HCC recurrence, including liver resection, radiofrequency ablation, or TACE, has been successfully used in selected patients with limited disease, and might be considered when technically feasible.[103] Sorafenib has been used with limited side-effects after liver transplantation, sometimes in conjunction with mTOR inhibitors, and might be considered when systemic treatment is warranted.[104] This topic is summarised in the last two recommendations: (36) HCC recurrence after liver transplantation may be treated by surgery for resectable lesions or by locoregional therapy or systemic therapy (including sorafenib) for unresectable lesions; (37) liver retransplantation is not appropriate treatment for recurrent HCC.

Conclusion

The 37 recommendations and statements presented here cover the most controversial topics surrounding liver transplantation for HCC, and may guide transplantation programmes around the world to improve management of their HCC patients. The phrasing of many recommendations permits adjustment according to variations in programme and regional circumstances, among which might be team experience and the availability of donor organs or living donation. Although the conference was not designed to address future areas of research, the existence of weak recommendations or absence of recommendation in a controversial area might serve as the basis to identify key questions that urgently require convincing answers.

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OLT for HCC consensus group

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Details of members of the expert panels, local organising committee, and writing committee can be found in the webappendix p1.

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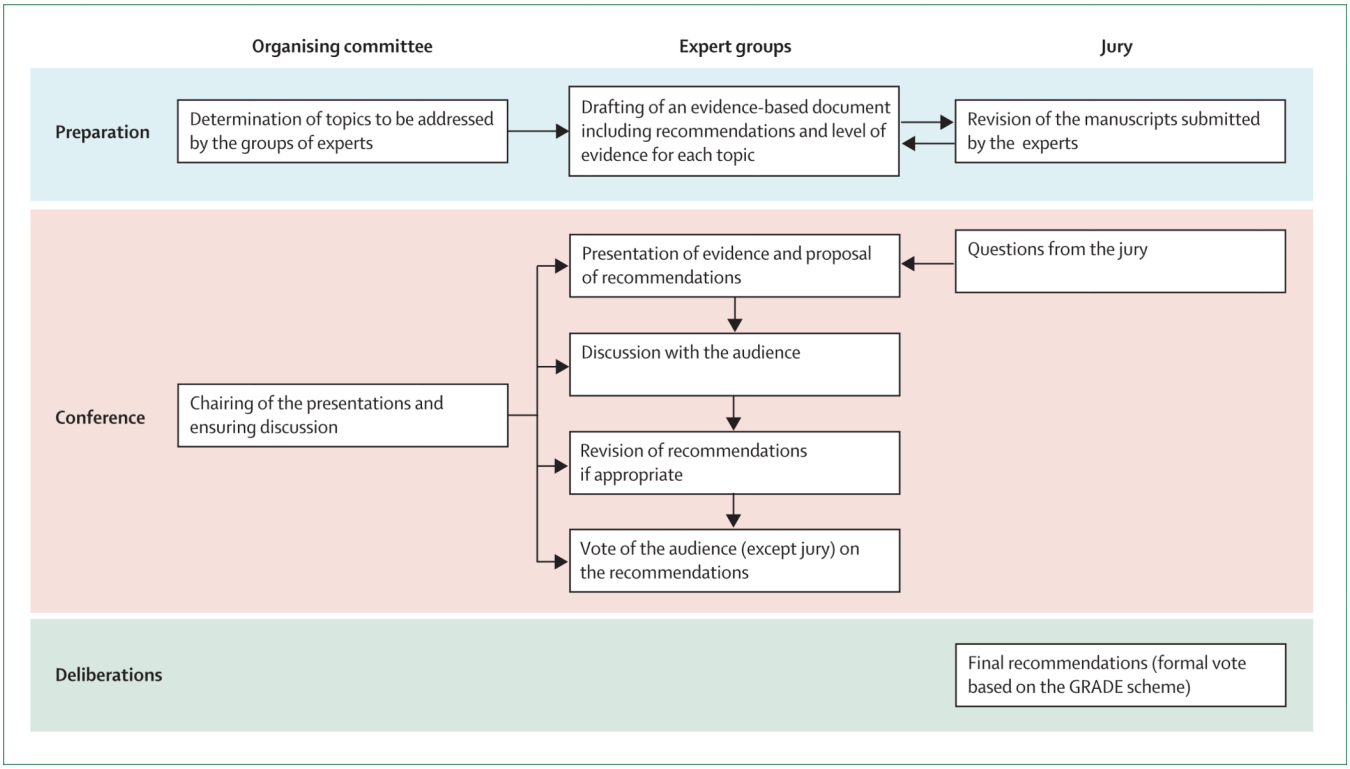

Figure 1. Format of the HCC consensus conference

The role of the organising committee, expert groups, and jury at each step of the conference. HCC=hepatocellular carcinoma. GRADE=grading of recommendations assessment, development, and evaluation.

Table 1

Summary of recommendations and statements

	Level of evidence	Strength of recommendation
Assessment of candidates with HCC for liver transplantation		
1. When considering treatment options for patients with HCC, the BCLC staging system is the preferred staging system to assess the prognosis of patients with HCC	2b (P)	Strong
2. The TNM system (7th edn) including pathological examination of the explanted liver, should be used for determining prognosis after transplantation with the addition of assessment of microvascular invasion	2b (P)	Strong
3. Either dynamic CT or dynamic MRI with the presence of arterial enhancement followed by washout on portal venous or delayed imaging is the best non-invasive test to make a diagnosis in cirrhotic patients suspected of having HCC and for preoperative staging	1b (D)	Strong
4. Extrahepatic staging should include CT of the chest, and CT or MRI of the abdomen and pelvis	3b (D)	Strong
5. Tumour biopsy is not required in cirrhotic patients considered for liver transplantation who have high-quality dynamic CT or MRI findings typical for HCC and a lesion larger than 1 cm according to current AASLD guidelines	1b (D)	Weak
6. For patients with lesions smaller or equal to 10 mm, non-invasive imaging does not allow an accurate diagnosis and should not be used to make a decision for or against transplantation	1b (D)	Strong
Criteria for listing candidates with HCC in cirrhotic livers for DDLT		
7. Liver transplantation should be reserved for HCC patients who have a predicted 5-year survival comparable to non-HCC patients	NA	Weak
8. Preoperative assessment of the size of the largest tumour or total diameter of tumours should be the main consideration in selecting patients with HCC for liver transplantation	2a (P)	Strong`
9. The Milan criteria are currently the benchmark for the selection of HCC patients for liver transplantation, and the basis for comparison with other suggested criteria	2a (P)	Strong
10. A modest expansion of the number of potential candidates may be considered on the basis of several studies showing comparable survival for patients outside the Milan criteria	3b (P)	Weak
11. Patients with worse prognosis may be considered for liver transplantation outside the Milan criteria if the dynamics of the waiting list allow it without undue prejudice to other recipients with a better prognosis	NA	Weak
12. α-fetoprotein concentrations add prognostic information in HCC patients and may be used for making decisions regarding transplantation in combination with imaging criteria	2b (P)	Weak
13. Biomarkers other than α-fetoprotein cannot yet be used for clinical decision making regarding liver transplantation for HCC	2b (P)	Strong
14. Indication for liver transplantation in HCC should not rely on microvascular invasion because it cannot be reliably detected prior to transplantation	2b (P)	Strong
Criteria for HCC candidates with non-cirrhotic livers		
15. The Milan criteria and its modifications are not applicable to patients with HCC developing in a non-cirrhotic liver. Such patients with non-resectable HCC and absence of macrovascular invasion and extrahepatic spread may be considered as appropriate candidates for liver transplantation	4 (P)	Weak
16. Patients with HCC in non-cirrhotic liver who were treated by resection, and have intrahepatic recurrence of HCC and no evidence of lymph node or macrovascular invasion, may be considered for salvage transplantation	4 (P)	Weak
Role of downstaging		
17. Transplantation may be considered after successful downstaging	5 (P)	Weak
18. Liver transplantation after successful downstaging should achieve a 5-year survival comparable to that of HCC patients who meet the criteria for liver transplantation without requiring downstaging	5 (P)	Strong
19. Criteria for successful downstaging should include tumour size and number of viable tumours	4 (P)	Strong
20. α-fetoprotein concentrations before and after downstaging may add additional information	4 (P)	Weak

	Level of evidence	Strength of recommendation
21. Based on existing evidence, no recommendation can be made for preferring a specific locoregional therapy for downstaging over others	NA	None
Managing patients on the waiting list		
22. Periodic waiting-list monitoring should be performed by imaging (dynamic CT, dynamic MRI, or contrast-enhanced ultrasonography) and α-fetoprotein measurements	5 (P)	Strong
23. Based on current absence of evidence, no recommendation can be made on bridging therapy in patients with UNOS T1 (≤2 cm) HCC	NA	None
24. In patients with UNOS T2 (one nodule 2–5 cm or three or more nodules each ≤3 cm) HCC (Milan criteria) and a likely waiting time longer than 6 months, locoregional therapy may be appropriate	4 (P)	Weak
25. No recommendation can be made for preferring any type of locoregional therapy to others	NA	None
26. Patients found to have progressed beyond criteria acceptable for listing for liver transplantation should be placed on hold and considered for downstaging	5 (P)	Strong
27. Patients with progressive disease in whom locoregional intervention is not considered appropriate, or is ineffective, should be removed from the waiting list	5 (P)	Strong
Role of LDLT		
28. LDLT is acceptable for HCC patients who have an expected 5-year survival similar to comparably staged patients receiving a deceased donor liver. In LDLT, careful attention should be given to psychosocial considerations regarding both donor and recipient	NA	Weak
29. LDLT must be restricted to centres of excellence in liver surgery and liver transplantation to minimise donor risk and maximise recipient outcome	NA	Strong
30. In patients following LDLT for HCC within the accepted regional criteria for DDLT, retransplantation for graft failure is justified	5 (P)	Weak
31. In patients following LDLT for HCC outside the accepted regional criteria for DDLT, retransplantation for graft failure using a deceased donor organ is not recommended	5 (P)	Strong
Post-transplant management		
32. Post-transplant monitoring may include 6–12 monthly contrast-enhanced CT or MRI imaging and α-fetoprotein measurements	5 (P)	Weak
33. There is currently insufficient evidence from clinical trials to base a recommendation for choosing the type or dose of immunosuppression therapy to influence the incidence of HCC recurrence or its prognosis	NA	None
34. Based on current evidence, no recommendation can be made on the use of mTOR inhibitors solely to reduce the risk of HCC recurrence outside clinical trials	NA	None
35. The current evidence does not justify the routine use of adjuvant antitumour therapy after liver transplantation for HCC outside of a controlled clinical trial	NA	Weak
36. HCC recurrence after liver transplantation may be treated by surgery for resectable lesions or by locoregional therapy or systemic therapy (including sorafenib) for unresectable lesions	4 (P)	Weak
37. Liver retransplantation is not appropriate treatment for recurrent HCC	NA	Strong

Level of evidence for each recommendation refers to the Oxford classification.[4] HCC=hepatocellular carcinoma. BCLC=Barcelona Clinic Liver Cancer. TNM=tumour, node, metastasis. P=prognosis. D=diagnosis. AASLD=American Association for the Study of Liver Diseases. NA=not applicable. OLT=orthotopic liver transplantation. UNOS=United Network for Organ Sharing. LDLT=living donor liver transplantation. DDLT=deceased donor liver transplantation.

Table 2

Staging systems for stratification of patients with hepatocellular carcinoma

	TNM (7th ed)	Okuda	CLIP	BCLC	JIS	GRETCH	CUPI	Tokyo
Year introduced	2010	1985	1998	1999	2003	1999	2002	2005
Liver function	No	Bilirubin, albumin, ascites	CTP class	CTP class, portal hypertension	CTP class	Bilirubin, alkaline phosphatase	Bilirubin, alkaline phosphatase, ascites	Bilirubin, albumin
Performance status	No	No	No	Yes, ECOG status	No	Yes, Karnofsky		No
Tumour burden	Number of nodules, tumour size, PV invasion, metastasis	Tumour > or <50% of liver	Tumour > or <50% of liver, PV invasion, metastasis	Number of nodules, tumour size, PV invasion, metastasis	TNM stage, define by LCSGJ	PV thrombosis	TNM stage	Number of nodules, tumour size
α-fetoprotein concentration	No	No	Yes, cutoff 400 ng/mL	No	No	Yes, cutoff 25 ng/mL	Yes, cutoff 500 ng/mL	No
Staging categories	I, II, III, IV	Score 0–4; stage I, II, III	0–6	0, A, B, C, D	0–5	Score 0–3 risk groups	Score 0–12; three risk groups	0–8
Other parameters							+/− symptom disease	

The Up-to-7 criteria system was not selected since it does not include clinical performance, liver function, or tumour markers. Furthermore, since the system is dependent on microvascular invasion, it is not clinically applicable. TNM=tumour, node, metastasis. CLIP=Cancer of the Liver Italian Program. BCLC=Barcelona Clinic Liver Cancer. JIS=Japan Integrated Scoring. GRETCH=Groupe d'Etude et de Traitement du Carcinoma Hepatocellulaire. CUPI=Chinese University Prognostic Index. CTP=Child-Pugh-Turcotte. ECOG=Eastern Cooperative Oncology Group. PV=portal vein. LCSGJ=Liver cancer study group of Japan.