In less than 30 years, liver transplantation (LT) has rapidly developed from a highly experimental and controversial procedure to one of the most successful stories in medicine. Nowadays, LT is a widely accepted treatment for select patients with hepatocellular carcinoma (HCC). Historically, HCC was a dismal disease amenable only to palliative therapies; a number of curative alternatives, including liver resection, locoregional therapies, and LT, have emerged. This evolution is associated with dramatic improvements in imaging techniques and the implementation of surveillance programs, which have facilitated the detection of many HCCs at an earlier stage when an effective treatment is feasible. In this context, LT is considered an optimal strategy that addresses both the underlying disease and the cancer, and HCC is currently the indication for LT in 25% and 35% of all cases in Europe and the United States, respectively. The need to obtain the optimal benefit from the limited number of available organs has prompted the maintenance of stringent selection criteria so that only those patients with early HCC, who have the highest likelihood of achieving long-term survival after LT, are listed. The indications for LT and the allocation of donor organs are, therefore, closely scrutinized by all LT stakeholders.

An international consensus conference on LT for HCC was held in Zurich, Switzerland on December 2-4, 2010. The aims of this conference were as follows: (1) establishing the state of the art for indications for LT in patients with HCC and (2) providing internationally accepted statements and guidelines for LT programs. This conference was endorsed and financially supported by 10 major international societies focusing on liver diseases or LT: the American Association for the Study of Liver Diseases, the American Society of Transplant Surgeons, the European Association for the Study of the Liver, the European-African Hepato-Pancreato-Biliary Association, the European Liver and Intestine Transplant Association, the International Hepato-Pancreato-Biliary Association, the International Liver Cancer Association, the International
Liver Transplantation Society, the Transplantation Society, and the Liver and Gastrointestinal Disease Foundation. The University of Zurich also provided financial support for this conference.

For this purpose, a novel format for the consensus conference, which was based on the Danish model, was developed. The organizing committee identified 19 specific questions, and these questions were grouped into 5 topics (Table 1). Nineteen working groups were created to address these questions; each group was composed of 4 to 6 experts from various fields of medicine, including surgery, gastroenterology, radiology, oncology, pathology, patient representation, health insurance, statistics, and ethics. These experts were selected on the basis of their scientific and clinical records, and their mission was to prepare evidence-based papers and draft recommendations. They were asked to follow the Oxford classification for levels of evidence (Table 2). Nine people from a variety of clinical and academic fields (not including any fields involving LT or HCC) were appointed to a jury, and this jury reviewed the submitted papers, commented on them, and made the final recommendations. As in the Danish model, the essential rule was that the final recommendations were to be drawn by the jury and not by the experts.

Eighteen months before the conference in Zurich, the various topics and the progression of the groups’ work were extensively discussed with the organizing committee and the members of the jury. For example, 3 workshops were held during 2009 and 2010 (2 at the annual meeting of the American Association for the Study of Liver Diseases in Boston and 1 at the meeting of the European Association for the Study of the Liver in Vienna); there, the chairs or representatives from each working group met with the organizing committee and the jury president or vice-president to evaluate and discuss the status of their work. Consequently, most papers, including the recommendations from the working groups, were assessed in advance by the jury. Most often, revisions were made to these papers before the conference.

Approximately 300 attendees from 5 continents were present at the consensus conference in Zurich. The chair of each working group delivered a 15-minute presentation that covered each specific question, and this was followed by questions first from the jury and then from the audience. Before the conference, the members of the jury used the experts’ texts to prepare some proposals for final recommendations that answered the 19 specific questions. These proposals were discussed during the conference, and they were modified at that time in response to the discussions. Afterwards, the audience was polled anonymously with an electronic voting system to determine the

| Part/Session | Question |
|--------------|----------|
| 1. General considerations: diagnosis | What is the goal of LT? |
| A | Is tumor biopsy necessary? |
| B | What is the best staging system for HCC? |
| C | What is the optimal imaging modality for staging HCC? |
| D | Where are we with the Milan criteria? |
| E | Which matters most: the number of tumors, the size of the largest tumor, or the total tumor volume? |
| F | Where do we stand with respect to the markers for microvascular invasion? |
| G | What information could molecular markers provide? |
| H | What are the criteria for orthotopic LT? |
| I | Should the listing criteria be different for an HCC patient with an otherwise normal liver? |
| 2. Indications for LT | |
| A | Is HCC treatment on the waiting list necessary? |
| B | Does a patient qualify for orthotopic LT after down-staging? |
| C | What are the tools for monitoring HCC on the waiting list (eg, alpha-fetoprotein level, tumor size, and biopsy) and after LT? |
| 3. Bridging therapy, down-staging, and monitoring on the waiting list | |
| A | Should we use living donor grafts for patients with HCC (ethics)? |
| B | Should the LT criteria be different for deceased donation and living donation? |
| C | Should we perform deceased donor LT after the failure of LDLT? |
| 4. LDLT | |
| A | What is the role of adjuvant therapy after LT for HCC? |
| B | Should we adapt it? |
| C | Should a patient undergo retransplantation because of HCC recurrence? |
| 5. Monitoring after LT | |
| A | What is the impact of immunosuppression on HCC recurrence? |
| B | Should we adapt it? |
| C | Should a patient undergo retransplantation because of HCC recurrence? |

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strength of each recommendation; the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system for decision making was used (Fig. 1). The jury met independently after the meeting to produce final recommendations, which were based on the papers submitted by the experts, the discussions, and the vote of the audience during the conference.

A committee was then established to write the consensus text. This writing committee was composed of the president, the vice-president, and a statistician from the jury as well as 3 members of the organizing committee. This text will be published in The Lancet Oncology.

This special issue of Liver Transplantation provides the 19 original reports from the working groups of experts. These reports were reviewed by the jury before the conference and subsequently were peer-reviewed according to the editorial process after their submission to Liver Transplantation. The questions that were posed to the experts were categorized as follows (Table 1):

1. General considerations: diagnosis.
2. Indications for LT.
3. Bridging therapy, down-staging, and monitoring on the waiting list.
4. Living donor liver transplantation (LDLT).
5. Monitoring after LT.

The first part of the conference focused on the survival goals for LT in patients with HCC and on the tools for establishing the diagnosis of HCC. Post-transplant survival was a matter of debate. The experts proposed lowering the 5-year survival rate to 50% because of patients’ personal benefits from LT. However, because of the shortage of donor organs and for consistency with the statement that the results of LT within the Milan criteria are the benchmarks, the jury concluded that LT should be reserved for HCC patients who have a predicted 5-year survival rate comparable to that of non-HCC patients. For the diagnosis of HCC, the jury endorsed the algorithm of the American Association for the Study of Liver Diseases, which is based on state-of-the-art cross-sectional imaging techniques (computed tomography or magnetic resonance imaging).

In the second part of the conference, the experts focused on the indications for LT and on the possible expansion of the accepted criteria for LT for HCC. Mazzaferro et al. provided an exhaustive review of the literature and analyzed 90 studies, which covered

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**TABLE 2. Levels of Evidence for Therapy Studies Proposed by the Oxford Centre for Evidence-Based Medicine**

| Level of Evidence | Grading Criteria |
|-------------------|------------------|
| 1a                 | Systematic review of randomized controlled trials (including meta-analysis) |
| 1b                 | Individual randomized controlled trial with narrow confidence intervals |
| 1c                 | All-or-none studies |
| 2a                 | Systematic review of cohort studies |
| 2b                 | Individual cohort study and low-quality randomized controlled trial |
| 2c                 | Outcome research study |
| 3a                 | Systematic review of case-control studies |
| 3b                 | Individual case-control study |
| 4                  | Case series, poor-quality cohort studies, and case-control studies |
| 5                  | Expert opinion |

NOTE: Adapted from the Oxford Centre for Evidence-Based Medicine.

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**DO YOU AGREE WITH THE RECOMMENDATION?**

Figure 1. GRADE system. The strength of each recommendation was determined by the vote of the audience and the jury.
15 years of experience with the Milan criteria. Germani et al.\textsuperscript{13} conducted a meta-analysis of 101 studies and assessed the effects of staging HCC with the size and number of nodules on posttransplant recurrence and survival. They concluded that the diameter of the largest nodule or the total diameter of all nodules is the best outcome predictor. This conclusion agrees with recent Organ Procurement and Transplantation Network data, which suggest that the total tumor volume and the alpha-fetoprotein level could be useful for selecting HCC patients for LT.\textsuperscript{18} Freeman’s group\textsuperscript{16} addressed the issue of using extended criteria (ie, criteria beyond the Milan criteria). Although evidence has accumulated for good outcomes for some patients beyond the Milan criteria, no definitive recommendations could be made. These strategies should be considered according to the local situation of each transplant center (ie, the availability of donor organs and the mortality rate for patients on the waiting list).

Treatment on the waiting list and the down-staging of larger HCCs were the topics of the third part of the conference.\textsuperscript{19–21} This group of experts supported the concept of down-staging, although the indications and the criteria for defining success still need to be standardized. Not surprisingly, none of the locoregional therapies showed any superiority. As for treatment on the waiting list, no therapy was recommended for United Network for Organ Sharing T1 tumors. For United Network for Organ Sharing T2 tumors, the experts suggested bridging strategies for patients likely to wait longer than 6 months to prevent the development of contraindications during the waiting period. All therapies were extensively discussed, and a marginal advantage was shown for radiofrequency ablation.

The fourth part, which dealt with the use of LDLT for HCC patients, triggered some controversial debates among the experts, the audience, and the jury.\textsuperscript{22–24} They discussed ethical concerns with the double equipoise describing the balance between the recipient’s survival benefit with or without LDLT and the risks of morbidity and mortality for the donor. Five years after the publication of the findings of the Vancouver forum,\textsuperscript{25} it is well accepted that patients with HCC within the Milan criteria should be offered LDLT as a treatment option. On the other hand, the question of offering LDLT to HCC patients beyond the accepted criteria raised many questions. There were arguments from experts in favor of donor protection and from experts who instead focused on the patient’s benefit (the issue of organ sharing does not apply to LDLT). Finally, the jury decided not to make any formal recommendations about the use of LDLT for HCC patients beyond the Milan criteria. Each transplant center should determine a clear policy with rigorous safeguards and inform the community about the expected outcomes.

Finally, the fifth part of the conference focused on management after LT and paid special attention to the risk of HCC recurrence after LT.\textsuperscript{26–28} The experts investigated whether immunosuppression regimens have an impact on HCC recurrence and whether they should be adapted in such an oncological context. Adjuvant therapies were also evaluated for their potential to reduce tumor recurrence post-LT and improve long-term survival. Finally, the different therapeutic options and their indications for HCC recurrence were discussed.

Overall, this consensus conference format led to objective evaluations of the most controversial topics in the field of LT for HCC by an independent jury. To the best of our knowledge, this is the first time that this format has been used in this field, in which strong opinions or dogmatic beliefs are usually difficult to challenge. The results of this effort are compiled in this special issue, which provides up-to-date information for the consensus text to be published in The Lancet Oncology.\textsuperscript{7}

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