SUPPLEMENT

Summary of Candidate Selection and Expanded Criteria for Liver Transplantation for Hepatocellular Carcinoma: A Review and Consensus Statement

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Liver transplantation (LT) is accepted as the standard treatment for select patients with hepatocellular carcinoma (HCC) and chronic liver disease. LT achieves oncological clearance and treats the underlying chronic liver disease. The gap between the demand for cadaveric organs and the supply necessitates the use of selection criteria to optimize the utilization of cadaveric grafts for patients with HCC. The use of these criteria must be carefully offset against the potential harm to existing patients without HCC who are also awaiting these scarce organs. Since the introduction and subsequent validation of the Milan criteria in 1996,[1] 5-year survival rates greater than 70% have been achieved internationally for patients satisfying the criteria (a solitary HCC with a diameter $\leq$ 5 cm or as many as 3 lesions with each diameter $\leq$ 3 cm and no macroscopic vascular invasion or extrahepatic disease). The Milan criteria are now widely accepted and are used as the standard selection criteria for the allocation of cadaveric organs for LT. An analysis of the outcomes of LT for HCC has, however, identified a subgroup of patients who do not satisfy the Milan criteria but nonetheless achieve excellent results. This has prompted a call for the expansion or revision of the selection criteria to optimize resource allocation. Here we review the key issues surrounding the expansion of the selection criteria that were identified at the 2010 International Consensus Conference on Liver Transplantation for Hepatocellular Carcinoma, and we present our recommendations for consensus statements.

Additional Supporting Information may be found in the online version of this article.

Abbreviations: AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; LDLT, living donor liver transplantation; LT, liver transplantation; OLT, orthotopic liver transplantation; OPTN, Organ Procurement and Transplantation Network; PIVKA-II, protein induced by vitamin K absence or antagonist II; QALY, quality-adjusted life year; SRTR, Scientific Registry of Transplant Recipients; TTV, total tumor volume; UCSF, University of California San Francisco.

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WHY SHOULD THIS SCARCE DONOR RESOURCE BE USED FOR PATIENTS WITH HCC?

A recent update from the Milan group showed that their excellent initial results were maintained in the long term; the 10-year survival rate was greater than 70% in a cohort of 300 patients who underwent transplantation for HCC. These results have been validated by a number of other studies, which have demonstrated 5-year survival rates greater than 70% for patients with HCC satisfying the Milan criteria.[2,3]

In order to assess the consumed resources versus the survival benefit gained with a given intervention, we can use the incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained.

There are no robust studies of the cost-effectiveness of LT for HCC. However, analyses of the cost-effectiveness of LT for other diagnoses suggest that LT results in an ICER in the range of $35,000 to $125,000.[4] In comparison, the accepted multimodal therapy for pancreatic cancer can result in an ICER of $300,000 to $400,000 per QALY gained (depending on the types of adjuvant treatments) in comparison with less aggressive treatments.[5]

Several studies have assessed the cost-effectiveness of living donor liver transplantation (LDLT) for early-stage HCC, and all have concluded that in comparison with waiting for a deceased donor organ or not receiving a transplant, the ICER for LDLT is usually less than $50,000 per QALY.[6]

Thus, using the limited data available, we conclude that for patients with HCC confined to the liver and within the accepted criteria, LT falls well within accepted survival benefit and cost ranges reported for treatments of other malignancies. Furthermore, this cost-effectiveness analysis does not take into account the costs of treating the underlying liver disease for HCC patients, which can be substantial, and this would further improve the ICER for LT for patients with HCC and underlying cirrhosis. Moreover, there are no comparative effectiveness analyses that address whether LT is more cost-effective when specific HCC criteria are met.

In the absence of high-quality, prospective, comparative studies, we summarize the recent relevant case series reported in the literature and present survival data for nonmalignant indications from the US Organ Procurement and Transplantation Network (OPTN). A literature review and OPTN data are presented in Supporting Appendices 1 and 2.

ARE THERE EXTENDED SELECTION CRITERIA?

The success of the Milan criteria has led to calls for their expansion beyond boundaries that some consider to be too restrictive. These arguments are strengthened by studies demonstrating excellent outcomes for patients who actually underwent transplantation outside the Milan criteria according to reviews of their explant pathology. There is a drive to develop extended criteria to identify these patients and increase the number of candidates eligible for LT.[7,8]

One fundamental limitation of all preoperative selection criteria that warrants an explicit discussion is radiological staging errors. Radiological understaging remains a significant problem; up to 20% of transplant patients within the Milan criteria have adverse histopathological factors (eg, poor differentiation and microvascular invasion) that increase the risk of recurrence in this subgroup. This highlights the shortcomings of using morphometric data as surrogate markers of tumor biology and the limitations of current modalities of preoperative staging.

In 2001, using expanded inclusion criteria, University of California San Francisco (UCSF) researchers demonstrated a tumor recurrence rate of 11.4% and 5-year survival rates of 72.4% in patients with T1 and T2 tumors and 74.1% in patients with T3 tumors. The new criteria included solitary tumors $\leq$ 6.5 cm in size or 3 or fewer tumors with the largest diameter $\leq$ 4.5 cm and the total tumor diameter $\leq$ 8 cm. These criteria were developed on the basis of explant pathology.[9] The UCSF group subsequently validated their expanded criteria with preoperative radiological staging.[10] Over a period of 5 years, 168 patients with HCC, including 38 patients who exceeded the Milan criteria but were within the new criteria, underwent transplantation. The 1- and 5-year recurrence-free probabilities were 95.9% and 90.9%, respectively, and the 1- and 5-year probabilities of survival without recurrence were 92.1% and 80.7%, respectively. These outcomes are comparable to those of other studies of patients undergoing transplantation within the UCSF criteria.[11,12]

Notably, there is a significant overlap between patients meeting the Milan criteria and patients meeting the UCSF criteria. The UCSF criteria result in a modest expansion of the number of eligible patients (estimated to be 5%-10%). The one exception to this can be found in a study by Duffy et al.[11] from the University of California Los Angeles. Four hundred sixty-seven patients underwent orthotopic liver transplantation (OLT) for HCC; only 173 (37%) were within the Milan criteria, and 185 were outside the Milan criteria but were within the UCSF criteria (40%). The survival outcomes were analyzed according to whether the subjects fell within the Milan criteria, within the UCSF criteria, or outside the UCSF criteria. There were no differences in overall survival or recurrence rates between the Milan and UCSF groups, regardless of whether radiological or pathological staging criteria were used to stratify the results.

Decaens et al.[13] evaluated the UCSF criteria in a large multicenter study, and they concluded that the application of the UCSF criteria resulted in an unacceptable 5-year survival rate less than 50%. From 1985 to 1998, 467 of the 479 patients listed for HCC (97.5%) underwent transplantation. Forty-four of these patients (9%) were outside the Milan criteria but

within the UCSF criteria. Based on the pre-OLT classification, an intention-to-treat analysis of this subgroup demonstrated a statistically nonsignificantly lower 5-year survival rate in comparison with patients within the Milan criteria (45.6% versus 60.1%, $P > 0.05$). Similarly the rates of recurrence were not statistically different between these groups. One major factor needs to be taken into consideration before the results of this study are interpreted. The study was conducted over a very long period extending from 1985 to 1998. The radiological and interpretation techniques of the first 10 years of the study were inferior to those used during the last 3 years. Thirty-four percent of the patients within the Milan criteria and 48% of those within the UCSF criteria were understaged for the whole period. However, when the data from the last 3 years were analyzed, 28% of the patients in the Milan group and only 8.3% of the patients in the UCSF group were found to be understaged. This problem with radiology has resulted in the disproportionate understaging of pre-OLT patients outside the Milan criteria but within the UCSF criteria, and this has contributed to the reported inferior outcomes. The conclusion that the UCSF criteria have limited clinical utility is, therefore, questionable.

Alternative criteria have been proposed by other centers. These include criteria from the Asan Medical Center in Korea[14] (as many as 6 nodules with each $\leq$ 5 cm in size); criteria from Hangzhou, China[15] [total tumor diameter $\leq$ 8 cm or $>$ 8 cm with grade I or II tumors and an alpha-fetoprotein (AFP) level $\leq$ 400 ng/mL]; criteria from the University Clinic of Navarra in Spain[16] (1 nodule $\leq$ 6 cm in size or 2-3 nodules with each $\leq$ 5 cm in size); and criteria from Kyoto, Japan[17] [up to 10 nodules with each $\leq$ 5 cm in diameter and a protein induced by vitamin K absence or antagonist II (PIVKA-II) level $\leq$ 400 mAU/mL]. Unfortunately, none of these criteria have been externally validated (a literature review is presented in Supporting Appendix 1).

The Metroticket concept states that the further you expand HCC staging criteria for LT, the greater the cost will be in terms of higher recurrence rates and poorer overall survival. This concept was developed so that we would have a simple predictive model for estimating the survival of patients undergoing LT with tumors beyond the Milan criteria according to the number and size of the tumors.[18] The model is based on an analysis of data for 1556 patients who underwent transplantation at 36 centers. Survival was correlated with the size of the largest tumor, the number of tumors, and the presence of microvascular invasion in explants. For 283 patients who fell within the up-to-7 criteria for HCC (ie, the sum of the largest tumor diameter in centimeters and the number of tumors is $\leq$7) and did not have microvascular invasion, the 5-year overall survival rate was 71.2%. One of the major drawbacks of this study is that the model is based on postexplant pathology criteria; therefore, histological criteria that are not available before LT (eg, microvascular invasion) are included in the prognostic model. The up-to-7 criteria were compared with the Milan criteria and the UCSF criteria in a pathological study of 479 explanted livers from 2 centers by D'Amico et al.[19] They reported 5-year recurrence rates of 14% within the criteria and 51% outside the criteria. Interestingly, a recurrence rate of only 24% was recorded for patients beyond the up-to-7 criteria as long as they had a favorable tumor pathology with no microvascular invasion or poor differentiation.

Tumor Number

An analysis of the published literature (mostly from LDLT groups) suggests that an expansion of the criteria in terms of the number of tumors has a minimal impact on outcomes principally because the number of tumors does not correlate with microvascular invasion.[20-22] Most studies have suggested that the number of tumors can be expanded up to 5. Using tumor markers such as PIVKA-II as a marker of tumor biology for LDLT, Ito et al.[17] suggested an extension of the criteria up to 10 tumors if all the tumors are less than or equal to 5 cm in diameter. A 5-year survival rate of 86.7% was achieved in this select group. At a median follow-up of 29 months, 12.8% of the patients with 4 to 10 tumors developed recurrence, whereas 17.6% of the patients with 3 or fewer tumors did.[17]

Tumor Size

The diameter of the largest tumor has been found to be a significant factor affecting outcomes. The principal reason for the negative correlation between the size and the outcome is the association between microvascular invasion and the risk of recurrence. The Metroticket study showed a linear correlation between inferior outcomes and the tumor size and microvascular invasion as the tumor size progressed beyond 5 to 6 cm.[23] The UCSF criteria extended the limit to 6.5 cm without an adverse impact on survival or recurrence.

Total Tumor Volume (TTV)

Discrepancies between radiological and pathological assessments for both the Milan criteria and the UCSF criteria prompted a search for more reliable morphometric data that could be used as selection tools. TTV was evaluated by Toso et al.[24] in a study of 3 centers. A preliminary analysis at 1 center was subsequently validated by the findings from the 2 other centers. A TTV of 115 cm^3 was used as the cutoff. More patients underwent transplantation within the novel TTV criteria versus the Milan and UCSF criteria without an adverse impact on survival or recurrence. The preoperative radiological accuracy increased to 91% (69% and 75% for the Milan criteria and the UCSF criteria, respectively). This concept was further tested by the same group in 6478 adult recipients from the Scientific Registry of Transplant Recipients (SRTR) database.[23] A score combining a TTV $>$ 115 cm^3 and an

AFP level > 400 ng/mL provided the best prediction of outcome and confirmed the findings of the initial study.

AFP

Several studies have highlighted the impact of AFP levels on outcomes after LT.[21,25,30] Various absolute cutoff values ranging from 200 to 1000 ng/mL have been proposed. AFP could be used as one of the tools for extended selection criteria. A recent study using SRTR data demonstrated the importance of AFP along with TTV as a predictor of recurrence and outcome.[21] In addition to criteria based on the size and number, an AFP level < 400 ng/mL was used by Ravaioli et al.[26] to select patients for LT after down-staging protocols. Vibert et al.[27] suggested that dynamic changes in AFP levels > 15 μg/L are the most relevant preoperative predictors of recurrence and overall survival (a literature review is presented in Supporting Appendix 3).

Response to Down-Staging

The response to down-staging can be used as a selection tool and as a surrogate marker of the tumor biology. Depending on the entry and transplant eligibility criteria, response rates ranging from 23.7% to 90% have been published in the literature.[28] The interpretation of these results is confounded by the extreme variations in the down-staging protocols, the types of ablative treatments, and the time periods between down-staging and transplantation.

Tumor Differentiation

Several studies have shown the influence of tumor differentiation on posttransplant outcomes, with poor differentiation closely correlated with microvascular invasion. In their report from the international HCC registry, Klintmalm et al.[29] proposed the use of tumor differentiation as an LT selection tool. In 2004, Cillo et al.[30] studied 48 LT patients with well or moderately differentiated tumors according to preoperative fine-needle aspiration biopsy samples (38% were beyond the Milan criteria); they achieved 5-year actuarial overall and disease-free survival rates of 75% and 92%, respectively. As a tool for selecting patients and predicting recurrence-free survival, Decaens et al.[13] proposed a preoperative score based on the tumor size, number, and differentiation. However, there seems to be a poor correlation between pre-LT biopsy findings and explant pathology findings, and this is most likely representative of tumor heterogeneity.

Radiological Staging

One of the biggest challenges in interpreting the published data is the variability of the sources of the tumor morphometric data used to define the various criteria.

The majority of the studies have used explant pathology data to assess the size and number of liver tumors; very few studies have validated these data against preoperative radiological analyses. Despite recent advances in radiological techniques, a misdiagnosis still occurs in up to 20% of cases, with staging errors occurring in 20% to 30% of cases. In a prospective study from UCSF, understaging occurred for 20% of stage II tumors and for 29% of stage III A tumors; other studies using United Network for Organ Sharing and SRTR data have estimated the overall accuracy of pre-LT HCC staging to be no better than 50%.[7,31]

The factors influencing overall survival and disease recurrence are summarized in Supporting Appendix 4.

Thus, if there were no constraints on donor resources, there is compelling evidence for LT as a treatment for HCC. Although numerous studies have stratified survival after LT by tumor characteristics, even for the more advanced cases, LT offers a better chance for a cure than any other treatment. However, it is well recognized that there is a severe mismatch between the number of available donor organs and the number of patients who could potentially benefit. For example, in the United States alone, in which HCC is only modestly prevalent in comparison with other regions, the estimated number of potential candidates with HCC who could benefit from LT is more than 20,000 per year; this number far exceeds the number of deceased donor organs procured per year (8000). The demand for organs and the conflicts between patients with HCC and patients with non-HCC indications are likely to be similar across the globe with some regional variations. These regional variations might be important for the extension of the criteria.

Data on the long-term outcomes after LT for HCC are lacking. In a recent report using the OPTN database, HCC patients had inferior long-term survival in comparison with patients with all other diagnoses. The 5-year overall survival rate for HCC patients was 56%, whereas the 5-year survival rate for all other patients undergoing LT was approximately 70%.[32] One could argue that these discrepancies should preclude the use of precious donor resources for patients with relatively poor outcomes in comparison with patients with other indications. However, these data suffer from historical bias because many of the patients included in these studies underwent transplantation before the establishment of policies that essentially restrict the allocation of donor livers to patients with HCC within the Milan criteria. Contemporary data suggest that 5-year survival rates for HCC patients ranging from 70% to 80% can be achieved after LT.[23,33]

The paucity of data addressing the survival benefits of LT for HCC and the limited cost-effectiveness analyses hinder our ability to draw meaningful comparisons. In fact, researchers reporting comparative effectiveness data for LT routinely exclude HCC patients from their analysis.[34,35] Moreover, there are no studies that account both for the costs and morbidity

associated with the neoadjuvant locoregional treatments often applied to candidates with HCC who are waiting for LT and for the costs and morbidity related to transplantation and follow-up care. Thus, although there are a large number of small single-center case series documenting post-LT survival rates similar to those achieved for benign indications, there are no comparative effectiveness studies and, consequently, no cost-effectiveness data with which we can make evidenced-based recommendations.

On the basis of these case series and the poorly controlled natural history survival data for untreated HCC, we conclude that there are likely benefits attributable to LT for patients with HCC meeting the Milan criteria. Because these results are similar to those of patients with nonmalignant diagnoses, using the scarce donor resource for candidates with HCC meeting the Milan criteria can be justified.

Much attention has been focused on the fact that posttransplant results for some patients with HCC beyond the Milan criteria are similar to those for patients meeting the Milan criteria. Other patients with more advanced disease have median survival times that are significantly less than those of patients within the Milan criteria and hence have the potential to gain increased survival benefits because they still achieve reduced but potentially acceptable results with LT. Consequently, in contrast to traditional rationales for surgical oncology, the potential for any survival benefit from an intervention used to treat an otherwise terminal cancer is not sufficient to establish that such an intervention is indicated because there are many other patients for whom the donor resource can provide a larger survival benefit. Some threshold of acceptable results similar to but not necessarily identical to the results that are achievable for other indications is essential. This distribution of organs from the donor pool to candidates with various levels of failure risk also applies to other indications for LT with a high recurrence risk (eg, hepatitis C virus).

WHAT ARE UNACCEPTABLE RESULTS FOR LT?

As previously highlighted, in most surgical oncology settings, even a small chance of a cure is an acceptable indication for the treatment. However, because the supply of donor organs is so limited and there are many other candidates for whom LT can offer a long-term survival probability greater than 70%, more than a small chance at success is required. The Metroticket concept was developed to offer a simple predictive model for estimating 5-year patient survival rates after LT for patients with tumors beyond the Milan criteria according to the number and size of HCC tumors.[23] The researchers who developed this model found that patients with HCC achieved a 5-year overall survival rate of 71.2% when 7 was the sum of the size of the largest tumor (in centimeters) and the total number of tumors. On the basis of these results, they suggested this method for determining an acceptable result threshold because this patient survival rate was similar to the rate found for LT recipients with HCC meeting the Milan criteria. Although this level of patient survival may be much higher than that generally accepted for other advanced cancer treatments, the results obtainable for the entire population in need of LT should influence the determination of an acceptable result threshold.

Because tumor size estimations based on current imaging technology are somewhat subjective, many have begun to explore the potential for more precise prognostic predictions with molecular techniques. None of these, however, have been subjected to rigorous statistical validation across patient types and treatment venues. In the future, molecular techniques will help us to understand the potential for tumors to be down-staged as well as the risk of recurrence after LT; however, we believe that they are not sufficiently standardized or validated to be clinically applicable to the selection of HCC candidates for LT at the present time.

Another way to define the acceptable threshold of success for LT for HCC is to measure the effects of assigning donor organs to candidates with increasingly advanced tumors versus the rest of the waiting list.

WHAT IMPACT DOES TREATING HCC PATIENTS WITH LT HAVE ON OTHER CANDIDATES FOR LT?

Because the number of donor organs is much smaller than the number of patients potentially treatable with LT and is relatively fixed, it is informative to consider the effects of assigning a larger proportion of the donor organs to a given population. In this instance, the determination of how much harm is bestowed on the waiting population by the assignment of more donor organs to patients with HCC depends on the risks that the remaining candidates face if they are forced to wait longer, and it is also influenced by the potential reduction in patient survival after transplantation that may occur with the assignment of more donor organs to patients with higher risks of HCC recurrence. This type of analysis was recently published by Volk et al.[36] Using data from the United States, they reported that on average, patients beyond the Milan criteria would need to achieve a 5-year survival rate of 61% or higher in order to not reduce the life years available to the entire population of LT candidates. In other words, offering more of the available donor organs to patients with HCC tumors beyond the Milan criteria would affect the other waiting patients negatively if the 5-year survival rate for the HCC patients undergoing transplantation were less than 61%. They also indicated that the effects on non-HCC patients waiting for LT would vary widely across the United States and depend on the probabilities of dying and undergoing LT in the various US regions.[36] Thus, in some areas, only if the 5-year survival rate were less

than 25% for LT for HCC would the remaining non-HCC candidates be harmed, whereas in other areas, the 5-year success rate for LT for HCC would have to exceed 71% in order to avoid harm to non-HCC candidates because the waiting-list dynamics and organ availability vary so widely across the United States. Interestingly, using the same type of approach, a group from Padua, Italy, reported that the 5-year survival rate for HCC patients receiving LT would need to exceed only 30% to avoid harm to the remaining patients.[37] These authors suggested that this was mostly due to the relatively low mortality rate on their waiting list. These studies are based on Markov models using transition probabilities gleaned from the available literature and sensitivity analyses to assess whether the modeled results are consistent when the transition probabilities are altered.

Although caution should be used in interpreting these studies because of the requirement for these assumptions, both summarized reports came to the same general conclusion. Non-HCC candidates waiting for LT are affected by the expansion of the selection criteria for HCC candidates in a manner proportional to the scarcity of deceased donor livers. If there is a relative abundance of liver grafts, the expansion of the HCC selection criteria will have much less effect on non-HCC candidates. In contrast, the liberalization of HCC selection criteria has a much more negative effect in areas where candidates have to wait longer or have higher mortality risks at the time of an organ offer because there are fewer deceased donor livers available.

Currently, evidence shows that patients meeting the Milan criteria have somewhat of an advantage on the waiting list in the United States. Using competing risk analyses, Washburn et al.[38] showed that patients within the Milan criteria had a lower chance of being removed from the waiting list because of disease progression or death in comparison with patients without HCC. Data from Japan[39] and San Francisco[9] suggest that most patients with early-stage HCC do not progress rapidly for approximately 1 year after they join the waiting list. The articles from Japan (n = 56) and San Francisco (n = 46) report single-center longitudinal studies in which a variety of temporizing ablative treatments were used and the progression of HCC beyond resectability or the UCSF criteria was recorded. These publications analyzed the dropout from the waiting list but censored patients who were removed for transplantation and thereby potentially overestimated the dropout rate. In the more recent report from Washburn et al., a competing risk analysis was used to better assess the competing outcomes (dropout, transplantation, and still waiting) for HCC candidates. The dropout rates were much lower for HCC patients versus adults with other diagnoses on the OPTN waiting list.

We conclude that giving any group of patients access to the donor pool potentially disadvantages the other candidates, particularly if the advantaged group has a lower mortality risk during the waiting period and a poorer survival rate after transplantation in comparison with the remaining wait-list population. Thus, as for all waiting candidates, the indications and prioritization for LT should be directed to patients who share similar survival benefit expectations. In general, criteria that define the indications for LT (HCC and non-HCC) should select candidates with similar survival characteristics. Therefore, the criteria for selecting patients with HCC for LT will depend on the availability of donor organs and the number of patients waiting with non-HCC disease in a given area, and they should not be defined as universal constants for every situation around the world. When waiting lists are small in comparison with the availability of donor organs, LT for HCC beyond the UCSF criteria will be acceptable because this will have relatively little impact on the other waiting patients and will still provide a survival benefit in comparison with no transplantation for patients with advanced or early HCC. In areas where donor organs are less available and/or waiting lists are longer or are filled with patients with more severe liver disease, the criteria for selecting HCC candidates for transplantation will need to be restricted to only earlier stage HCC because expanding the selection criteria further will necessarily have a negative impact on the outcomes of patients with benign liver disease on the list.

SHOULD THE CRITERIA FOR TREATING HCC PATIENTS WITH LT BE BASED ON INDIVIDUAL NEED OR OVERALL OUTCOMES?

In our opinion, LDLT is a different radical treatment option that does not have an impact on the deceased donor resources available to patients on the waiting list. In addition to influencing recipient outcomes, LDLT also raises issues of health increments and decrements for living donors that need to be taken into account when the ICER is being assessed. Preliminary estimations of the cost-effectiveness of LDLT with Markov models and sensitivity analyses suggest that LDLT can also provide acceptable increments for the ICER, even when we account for donor morbidity and mortality.[40] To some degree, these estimates are dependent on assumptions of donor morbidity, mortality, and costs that could change with more experience. This suggests a need for separate ethical and clinical arguments for expanding the criteria for performing transplantation in HCC patients with grafts from living donors, especially because these estimations are based on decision analysis models, which usually are not considered high levels of evidence.

In the case of LDLT for advanced HCC, the constraints of the deceased donor pool do not factor into the criteria for LT candidate selection. Offering LDLT to patients whose long-term survival is significantly reduced in comparison with patients with benign liver disease does not affect the other candidates waiting for a deceased donor because the living donor is not available to the remaining waiting patients. In the

LDLT scenario, the indication for LT for HCC is dependent on the willingness of the living donor to assume risks to his or her own health in order to be able to provide treatment to another person who has a disease that may impose a limited long-term outcome. This again becomes a relative ethics matrix, and the treatment of other cancers (eg, pancreatic cancer) can be used for comparison. Although no other individual assumes risks when a patient with pancreatic carcinoma is offered treatment, generally accepted principles of surgical oncology (not evidence-based medicine) dictate that there should be at least a 20% chance of a cure. Whether an expectation of a 20% success rate is acceptable for allowing living donors to assume the 0.5% to 1.0% mortality risk of donation has not been established. Even more in question is what degree of donor autonomy should be allowed in this decision. Should a motivated and willing living donor be prevented from donating to his or her loved one with HCC because the estimated survival rate after LT is less than 50%, less than 40%, or less than 20%? These questions have not been (and likely will not be) resolvable by meta-analyses or large randomized controlled trials. When deceased donor organs are relatively plentiful, expanding LT to HCC patients with more advanced tumors will not have a significant impact on the other waiting candidates. In these scenarios, LDLT should be rare because the deceased donor pool will allow the transplantation of more advanced cases in agreement with the survival benefit approach (treatment, even if it has a higher risk of failure, is still warranted because the alterative is so dismal). Conversely, in areas in which deceased donor organs are relatively scarce, patients with less advanced tumors and those with advanced tumors can be considered for LDLT if the donor is willing to assume the risks to his or her own health for whatever outcome is predicted on the basis of the tumor characteristics. This is possible because the living donor does not provide a resource for the entire population in need of LT but directs the donor organ to a single patient.

This discussion outlines the 2 sides of this question: the needs of the individual (almost any treatment is better than no treatment for HCC and is, therefore, justified) and the benefit to the population (the majority of the patients on the waiting list have a potential for survival with transplantation that is similar, if not superior, to that for patients with HCC). We conclude that a balance must be struck that provides an equitable probability of being treated to patients with HCC who have survival expectations similar to those of other candidates after transplantation. We believe that whatever HCC stage defines these survival expectations should be used as the basis for defining the indication for LT for HCC. The available data suggest that some patients with HCC beyond the Milan criteria fall within this definition. More precisely, the characterization of these patients (potentially with molecular fingerprinting of larger HCC lesions that are less aggressive) should be the focus of future research and is essential for improving the transparency of liver allocation policies. These more precise definitions and more transparent selection and outcome results will be critical to ensuring that HCC patients are selected according to objective criteria that are applied uniformly.

SUMMARY

The evidence base is poor overall because of the limited sample sizes of most studies and the heterogeneous cohorts and variables, and few have well-planned and statistically valid study designs. No studies have accounted for the effects of underlying liver diseases either before or after LT on overall outcomes, and only a few studies have assessed the effects of adjuvant treatments before transplantation. In the majority of the reports, the follow-up time is not sufficient for assessing 5-year survival rates. Many have used histological findings from explanted livers to stage patients, but this has little utility for preoperative staging and selection for LT. The presence of vascular invasion, the tumor number and size (also calculated as the TTV), and the AFP level have most consistently been associated with increased recurrence rates and diminished survival after LT. Most studies have reported acceptable survival rates for patients meeting the UCSF criteria; however, it is notable that there are documented survival rates for patients with HCC tumors beyond the UCSF criteria that would be more than acceptable in any other surgical oncology setting. It is the potential to affect candidates without HCC who are also competing for the limited pool of donor organs that limits the criteria for selecting patients with HCC for LT, especially when we consider LT for patients with more advanced stages of HCC.

RECOMMENDATIONS

1. There is no high-grade evidence for recommending a specific set of criteria for selecting patients with HCC for LT. The Milan criteria have been most widely used and have the most available evidence (although the quality is limited). They have become the benchmark for HCC selection (evidence level 2, recommendation grade B).
2. A modest expansion of the number of potential candidates is warranted because of several studies showing comparable survival rates for patients outside the Milan criteria. However, any expansion beyond the Milan criteria will have a negative impact on other LT candidates who do not have HCC, and the degree to which this affects the waiting list will depend on local waiting-list dynamics and donor organ availability (evidence level 3, recommendation grade B).
3. Among all the extended criteria that have been proposed, only the UCSF criteria have been prospectively validated, and the outcomes have been confirmed by other retrospective studies (evidence level 3, recommendation grade B).

4. There is some evidence for expanding the criteria as follows: increasing the number of tumors up to 5, considering a waiting time of 3 to 6 months after the down-staging of more advanced tumors, and selecting HCC candidates for LT with serum AFP levels < 400 ng/mL (evidence level 3/4, recommendation grade C).
5. There is a need to develop an evaluation of the health economics of LT for HCC similar to those available for other malignancies and other indications for LT.
6. There is a need to evaluate and develop tumor biology markers, which include imaging modalities (eg, positron emission tomography/computed tomography), molecular profiling, and serological markers (eg, PIVKA-II and des-gamma-carboxyprothrombin), in future studies of extended criteria. Gene signatures that drive the initiation, maintenance, and progression of HCC, which are expected to be helpful in classifying the tumor stages, metastasis, recurrence, and prognosis after resection, have been investigated.

The use of preoperative biopsy to determine the histological grade has been advocated and would provide tissue before LT for molecular analyses used to determine the risk of recurrence or, crucially, microvascular invasion. Potential molecular candidates include p53, T-cell lymphoma invasion and metastasis gene and Ras-related C3 botulinum toxin substrate 1, p21/WAF1 and murine double minute 2, c-Jun N-terminal kinase 1, mammalian target of rapamycin, and hepatic stem cell–like HCC. Various chromosomal aberrations, fractional allelic imbalances, DNA methylation, and gene expression profiles have also been proposed as prognostic tools for HCC. Although all these biomarker and molecular studies are on a relatively small scale and have not been incorporated into standard tumor-node-metastasis staging systems, they hold promise for accurate prognostication in the future.

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