Liver Transplantation for Hepatocellular Carcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference

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Abstract. Liver transplantation (LT) offers excellent long-term outcome for certain patients with hepatocellular carcinoma (HCC), with a push to not simply rely on tumor size and number. Selection criteria should also consider tumor biology (including alpha-fetoprotein), probability of waitlist and post-LT survival (ie, transplant benefit), organ availability, and waitlist composition. These criteria may be expanded for live donor LT (LDLT) compared to deceased donor LT though this should not adversely affect the double equipoise in LDLT, namely ensuring both acceptable recipient outcomes and donor safety. HCC patients with compensated liver disease and minimal tumor burden have low urgency for LT, especially after local-regional therapy with complete response, and do not appear to derive the same benefit from LT as other waitlist candidates. These guidelines were developed to assist in selecting appropriate HCC patients for both deceased donor LT and LDLT.

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INTRODUCTION

Liver transplantation (LT) offers excellent long-term outcome for certain patients with hepatocellular carcinoma (HCC), with a recent push to incorporate markers of tumor biology into selection criteria, rather than simply focusing on tumor size and number. In this working group report, we discuss how selection criteria and acceptable posttransplant outcomes for HCC patients undergoing living donor LT (LDLT) versus deceased donor LT (DDLT) should be different along with the optimal surgical management of patients presenting with a solitary small HCC. The aim of this guideline, approved by the International Liver Transplantation Society, is to provide a collection of expert opinions, consensus, and best practices surrounding LT for HCC. Intended for use by physicians, these recommendations support specific approaches to the appropriate use of both deceased donor and live donor LT in the management of patients with HCC.

DECEASED DONOR LT FOR HCC

Selection Criteria

LT remains the optimal treatment strategy for patients with early-stage HCC. LT is thought to be the best oncologic resection, replaces the diseased liver, and restores normal hepatic function. For patients with HCC exceeding the Milan criteria[1] (1 lesion ≤5 cm or 2–3 lesions ≤3 cm), survival after LT incrementally decreases with increasing

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tumor size and number[2] although modest expansion of tumor size criteria to increase access to LT can achieve post-LT survival comparable to the Milan criteria.[3–10]

Especially in areas with organ shortages, the pendulum has largely swung away from expanded criteria for several reasons. These include an emphasis on performing LT in those HCC patients most likely to derive significant transplant survival benefit,[11] concerns that implementation of expanded tumor criteria could reduce access to LT for patients with better post-LT prognosis,[12,13] and longer wait times leading to increased use of local-regional therapy (LRT) as a bridge to LT.[14] There is also mounting evidence that tumor burden is just one of many factors that predict post-LT outcome.[15,16] In this context, selection criteria have begun to shift to include surrogates of tumor biology (eg, alpha-fetoprotein [AFP]) and response to LRT, with a number of pre-LT selection criteria recently proposed.[2,17–22]

Recommendations

1. Indications for LT in HCC are aimed to cure cancer and improve patient's survival and quality of life (quality of evidence: moderate; strength of recommendation: strong).
2. Selection criteria should consider tumor biology (including AFP), tumor size and number, probability of survival, transplant benefit, organ availability, waitlist composition, and allocation priorities (quality of evidence: low; strength of recommendation: strong).
3. LT is recommended as a first-line option for HCC within Milan criteria, unsuitable for low-morbidity resection and ablation (quality of evidence: moderate; strength of recommendation: strong).
4. Consensus on expanded criteria for LT in HCC has not been reached but composite criteria that consider surrogates of tumor biology and response to neoadjuvant treatments, are likely to replace conventional morphological criteria for defining transplant feasibility (quality of evidence: moderate; strength of recommendation: strong).

PREDICTION MODELS FOR DDLT

Most pre-LT prediction models have incorporated serum makers in addition to various tumor burden cutoffs to more accurately determine recipient benefit. Post-LT survival begins to decline at an AFP of ~20 ng/mL[23,24] with worse survival as AFP increases. Therefore, various cutoffs have been utilized for exclusion from LT including >400[17] and >1000 ng/mL in the United States.[18] Patients with an elevated AFP who have a biochemical response to LRT have significantly better post-LT outcome than AFP nonresponders.[25,26] Additional serum marker cutoffs associated with inferior post-LT outcome include neutrophil-to-lymphocyte ratio >5, AFP-L3 >35%, and des-γ carboxyprothrombin >7.5 ng/mL[19,27,28] though these findings have not yet been validated. Several prediction models that allow for LT in HCC patients beyond Milan criteria require tumor biopsy and exclude patients with poorly differentiated tumor grade. With this approach, studies from Padova,[29] Toronto,[21] and Hangzhou[30] have shown acceptable post-LT survival in HCC patients beyond Milan criteria. One caveat is that the overall agreement of preoperative needle core biopsy with explant histopathology is relatively poor.[31,32]

Recommendations

1. Prognostication of post-LT outcome in patients with HCC, especially those beyond Milan criteria, should be based on measurable pre-LT conditions. Accuracy should be assessed in external independent prospective cohorts (quality of evidence: moderate; strength of recommendation: strong).

DOWNSTAGING/BRIDGING TREATMENTS FOR DDLT

LRT is frequently used with the aim of controlling tumor growth and reducing the risk of waitlist dropout, thus serving as a "bridge" to LT. While evidence supporting these bridging treatments in reducing waitlist dropout is limited, this approach seems justified when the waiting time for LT is expected to be at least 6 months.[13] Those who exhibit tumor progression despite LRT have significantly worse post-LT outcomes when compared to those who demonstrate treatment response or stable disease following LRT.[15,33–35] Observing tumor behavior over time after LRT may therefore allow for a more refined selection of candidates for LT.[36,37]

The goal of downstaging is to reduce tumor size so that the residual viable tumors fall within acceptable LT criteria with most published studies using the Milan criteria as the endpoint of downstaging.[38,39] The principle behind downstaging is to serve as a selection tool for a subset of patients with HCC beyond conventional LT criteria who would respond to downstaging treatments and do well after LT. This rationale is supported by the observation that post-LT outcomes in those successfully downstaged to Milan criteria are not significantly different from those who meet Milan criteria at presentation.[40,41] There is also correlation between successful downstaging and a low prevalence of unfavorable explant histologic characteristics.[40,42] In the United States, in an effort to standardize criteria for downstaging, the University of California, San Francisco downstaging protocol[40] has recently been adopted as a national policy for granting priority listing for LT. The initial selection criteria are single lesion ≤8 cm, or 2–3 lesions <5 cm with total tumor diameter <8 cm, or 4–5 nodules all <3 cm with total tumor diameter <8 cm. The application of downstaging also involves a minimum observation period of 3 months of disease stability from successful downstaging to LT.[38,40]

The use of more liberal inclusion criteria may result in a lower rate of successful downstaging and a higher rate of waitlist dropout,[43,44] as well as inferior post-LT survival.[45] In a recent analysis using the United Network for Organ Sharing database,[45] Mehta et al observed similar 3-year post-LT survival among patients with HCC always within Milan criteria (83%) compared to the group successfully downstaged using the above inclusion criteria (79%). In contrast, the 3-year post-LT survival was significantly lower at 71% in the "all-comers" downstaging group with initial tumor burden beyond these criteria.

There are obviously safety concerns related to downstaging, including hepatic decompensation following LRT. It has been proposed that only patients with adequate hepatic function (Child's A/B, bilirubin ≤3 mg/dL) should undergo downstaging,[38] based on recommended guidelines for transarterial chemoembolization.[46] Transarterial chemoembolization is the most commonly used treatment

modality in published series[38,39] and remains the recommended first-line treatment for downstaging. Y-90 radioembolization has shown promise as a downstaging treatment but requires further study.[47]

Recommendations

1. Although selection bias is likely, patients with HCC listed for LT receiving bridging therapies with objective response demonstrate improved waitlist and posttransplant outcomes (quality of evidence: moderate; strength of recommendation: strong).
2. Patients beyond Milan criteria can be considered for LT after successful downstaging, within defined protocols (quality of evidence: moderate; strength of recommendation: strong).
3. Tumor burden and tumor biology are good predictors of successful downstaging of HCC. Eligibility to downstaging should be defined upfront. In case of response, a no-treatment period to assess end-treatment sustainability is recommended (quality of evidence: moderate; strength of recommendation: strong).
4. The degree of tumor response to bridging treatment may help in defining LT priority in patients listed with HCC (quality of evidence: moderate; strength of recommendation: strong).

LIVE DONOR LT FOR HCC

Selection Criteria/prediction Models for LDLT

Guided by strong recent evidence, the majority of centers now use a combination of morphological (eg, Milan,[1] UCSF criteria[3]) and biological criteria to allocate livers for DDLT in patients with HCC, to select those that will benefit most from LT. However, in the "no competition" situation with LDLT, the ethical as well as scientific grounds have shifted. Several expanded criteria for LDLT have been proposed, although none have been externally validated.[30,48–54] The question that still remains is how far LT criteria can be expanded without adversely affecting the double equipoise in LDLT, namely ensuring both acceptable recipient outcomes and donor safety.[55]

Some predictive models incorporating tumor biology in selection criteria combining tumor burden, biomarkers, and ^{18}F-FDG PET avidity have been reported in the LDLT setting, including the National Cancer Center Korea and Japanese criteria.[28,56–60] One interesting aspect regarding selection criteria is that centers with longer wait times use downstaging/response to LRT by necessity whereas centers which primarily perform LDLT and have short wait times tend to have fairly liberal tumor burden criteria but rely heavily on biomarkers and/or negative ^{18}F-fluorodeoxyglucose positron emission tomography scan. FDG-negative patients beyond Milan criteria have satisfactory post-LT outcome[56,58–60] whereas those with a tumor to nontumor ratio >2 tend to do poorly. In the future, molecular criteria (eg, angiotensin 2, VEGF, miR-718, pERK, glycipan 3, osteopontin) may take center stage.[61,62]

Recommendations

1. Selection criteria for patients with HCC may be different in LDLT than DDLT in selected cases (quality of evidence: moderate; strength of recommendation: strong).
2. Selection of patients outside standard criteria for LDLT may use validated criteria based on AFP and DCP cutoffs (eg, <400 and <7.5 ng/mL, respectively),^{18}F-FDG PET nonavid tumor, and if applicable, response to LRT to ensure acceptable tumor biology. They should have no extra hepatic disease and/or macrovascular invasion (quality of evidence: moderate; strength of recommendation: strong).

Defining Minimal Survival Benefit Combined With Donor Risk

Attempting to maximize recipient benefit while minimizing donor risk reflects the basic tenet of achieving double equipoise.[55,63,64] There are perceived risks of transplanting patients with HCC too quickly without a minimal period of observation for tumor progression, as illustrated in the "fast-tracking" and "ablate and wait" concepts.[36,65] Additionally, there has been concern that graft regeneration in LDLT could lead to tumor growth and recurrence. However, several series and a meta-analysis have shown that LDLT achieves comparable outcomes to DDLT in HCC, thus largely negating these concerns.[66,67]

Previous reports have proposed an acceptable minimum survival of 50% at 5-year after LDLT for HCC.[68] An International HCC Consensus Conference report from 2012[13] suggested that expansion beyond Milan criteria should take into account the effect of delaying LT for all potential waitlist candidates, including the ones with nontumor indications. Hence, the resulting proposal was to reserve LDLT for HCC patients who have an expected survival comparable to that of non-HCC patients (ie, 70%–80% at 5 y). Using a Markov model, Volk et al[12] showed that the adverse effects of expanding LT criteria would outweigh its benefits if the expected 5-year overall survival of a patient transplanted outside Milan criteria was <61%. Taking each of these previous reports into consideration, we believe that a minimum 5-year post-LDLT survival of 60% is an acceptable benchmark.

The triple (triangular) equipoise concept elaborates on the balance of 3 ethical dimensions—donor safety, expected recipient outcome, and recipient need.[69] The risk of death for a recipient with a LDLT option is approximately half that of a patient awaiting DDLT without live donor options[70] and this risk falls even further if an HCC patient with an LDLT option has a MELD score >15.[71] Hence, it seems clear that HCC patients benefit from and deserve LDLT, especially in areas where DDLT rates are low.[72] Similar to the paradigm with DDLT, the "transplant benefit" principle[73] is a key concept for LDLT. By prioritizing patients based on life-years gained with LT, the transplant benefit principle performs better than urgency and utility schemes from a population perspective.[74]

In terms of donor risk, a worldwide survey with 11 553 liver donors reported a mortality of 0.2%, transplant rate of 0.04% for donor liver failure, and an overall donor morbidity of 24%.[75] An overall donor complication rate of <27% with <6% Clavien-Dindo grade 3/4 complications has been considered acceptable in a benchmark study.[76] However, we believe that centers should aim for zero donor mortality with maximum acceptable live donor risk of <20% for Clavien grade I/2 complications and <5% for grade 3/4 complications.[77]

Recommendation

1. Minimum acceptable recipient overall survival should be 60% at 5 years after LDLT (quality of evidence: moderate; strength of recommendation: strong).
2. The goal live donor risk should be a Clavien 1/2 complication rate <20% and 3/4 rate <5% aiming for zero donor mortality (quality of evidence: moderate; strength of recommendation: strong).
3. The donor should be informed about the recipient's prognosis based on established criteria, center results, and published evidence (quality of evidence: low; strength of recommendation: strong).

Role of Tumor Downstaging in LDLT

Whereas the "ablate and wait" policy is relevant in DDLT, its applicability for LDLT is questionable. Downstaging tumors from beyond to within conventional criteria has been demonstrated to improve outcomes in HCC patients following LT[39–42] though most downstaging studies have been primarily in the DDLT setting. Only approximately 60% of patients with HCC beyond conventional downstaging criteria (so-called "all-comers") can be successfully downstaged to Milan criteria with LRT.[43] Therefore, UCSF criteria may be a more achievable downstaging endpoint before LDLT. Although some case series have reported successful downstaging of HCC with portal vein tumor thrombus often using Y-90 radio-embolization,[78–81] the small number of patients and limited follow up make it difficult to propose guidelines for LDLT in this population at present.

Recommendations

1. HCC patients with tumor size and number beyond their "local" criteria should be downstaged with LRT at least to within UCSF criteria with AFP <500 ng/mL before LDLT. An observation period of at least 3 months after successful downstaging is suggested before LDLT (quality of evidence: moderate; strength of recommendation: strong).

MANAGEMENT OF SINGLE, SMALL HCC

Liver Transplantation Versus Hepatic Resection

Hepatectomy for early-stage HCC is increasingly being performed due to both increased HCC incidence and organ shortages, and offers 5-year survival rates up to 60%.[82] There are no randomized control trials evaluating resection versus LT, leading to the ongoing debate of which is most appropriate for patients within Milan criteria and adequate liver function. Resection confers up to 10-fold higher odds of recurrence compared to LT[1,83,84] and underlying cirrhosis increases recurrence risk after resection compared to normal background liver.[85] In patients without significant fibrosis, resection is universally advised as first-line treatment, but in patients with compensated cirrhosis, recommendations are mixed and vary by tumor size and number.[86]

In patients otherwise eligible for LT, postresection 5-year recurrence-free survival is 40%–50%.[87,88] While 10-year overall survival is better with LT for resectable HCC,[89] many studies have shown similar 5-year overall survival for resection compared to LT in patients with a single <3 cm HCC.[89,90] Patients with a single <3 cm HCC have improved outcome compared to those with larger tumor burden regardless of resection versus LT.[91–93] More recently, a large multinational study[94] reported a ~40% cure rate with resection (compared to 75% with LT) in patients with single <3 cm HCC and MELD <11 with similar intention-to-treat survival given the expected 10%–20% waitlist dropout rate in those awaiting LT.

The question of offering LT to resectable, Child's A patients with single small HCC takes on greater importance after Berry and Ioannou[95] found that HCC patients derive a significantly lower survival benefit from LT than non-HCC patients. Further, several studies have shown that HCC patients with favorable tumor (single tumor <3 cm and AFP ≤20 ng/mL) and liver-related characteristics (Child's A cirrhosis and MELD-Na <15)[11,96,97] have reduced urgency for LT. Such patients who subsequently undergo LRT with complete radiographic response have a very low risk of waitlist dropout[11,96,98] and thus exceedingly low LT urgency with decreased LT survival benefit.[37] This is especially true for HCC patients unlikely to have liver disease progression (eg, due to effective antiviral treatment or alcohol abstinence) and thus no alternate indication for LT.

Recommendations

1. HCC patients with compensated liver disease and minimal tumor burden have a low risk of waitlist dropout and do not derive the same immediate benefit from LT as other waitlist candidates (quality of evidence: moderate; strength of recommendation: strong).
2. Particularly in areas of organ shortages, due to competition with patients with higher transplant benefit, deceased donor LT is recommended only as second line treatment in resectable patients with single <3 cm HCC in case of tumor recurrence or liver failure after resection or ablation (quality of evidence: moderate; strength of recommendation: conditional).
3. Patients with well-compensated disease and single <3 cm HCC with complete response to LRT have reduced the urgency for LT (quality of evidence: moderate; strength of recommendation: strong).

Salvage Liver Transplantation

For patients undergoing resection, the strategy of salvage LT (SLT), or performing LT after recurrence within conventional transplant criteria, appears effective in 50%–60%[99,100] with intention-to-treat survival >80% at up to 10 years in patients who either do not recur after resection or who undergo LT after recurrence.[99] Importantly, having early-stage HCC at resection predicts success with the SLT strategy.[99] Similarly, Lee et al[101] found that initial disease within Milan, single tumor, and lack of lymphovascular invasion predicted decreased likelihood of postresection recurrence beyond Milan criteria. Patients with single <3 cm HCC would be expected to only have a 10-30% chance of recurrence beyond Milan and would likely be candidates for SLT in case of recurrence. Additionally, a recent systematic review and meta-analysis[102] found improved 5-year post-LT survival after SLT compared to primary LT and concluded that SLT may be a better treatment strategy for recurrent HCC in compensated

patients initially eligible for resection. While unlikely to apply to most patients with a single, small HCC, proposals to perform LT after resection in patients with a high risk for recurrence (eg, microvascular invasion and/or previously undiagnosed satellite lesions)[103,104] require further validation.

Recommendations

1. Patients with single <3 cm HCC who undergo resection but have tumor recurrence are highly likely to be eligible for SLT (quality of evidence: moderate; strength of recommendation: strong).
2. SLT and primary LT appear to have equivalent outcomes from the time of LT (quality of evidence: moderate; strength of recommendation: strong).

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