Liver transplantation as therapy for hepatocellular carcinoma

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Abstract
Liver transplantation can provide curative therapy in selected patients with hepatocellular carcinoma. Well-established criteria include tumours that are within the Milan criteria and without evidence of vascular or extrahepatic involvement. Modest expansion of the original Milan criteria has been shown to achieve similar recurrence-free survival rates. Overall, HCC recurrence occurs in about 10%-15% of LT recipients, most within the first 2 years. Predictors of post-transplant recurrence include high alpha-fetoprotein, macrovascular invasion, as well as tumour size and number. Once HCC recurs after transplantation, prognosis is poor, though better if detected early. There is no established role for systemic prophylactic post-transplant chemotherapy.

1 | INTRODUCTION

Liver transplantation (LT) was established as an effective therapy for small, hepatocellular carcinoma (HCC) in a landmark study by Mazzaferro and colleagues in 1996. Candidates had a single lesion no larger than 5 cm, or up to three lesions, no larger than 3 cm, without macrovascular invasion or spreading outside of the liver and survival was similar to that in patients transplanted without HCC.1 Although the “Milan criteria” are extensively applied in transplant centres, many have expanded the criteria to provide more patients with treatment options while maintaining acceptable recurrence-free transplant survival. HCC is the indication for approximately 30% of the LT performed in the US and Europe.

2 | SELECTION OF BEST CANDIDATES FOR LIVER TRANSPLANTATION

The goal of allocation strategies is to minimize wait-list deaths while achieving acceptable post-LT graft and patient survival. With the well-recognized shortage of donated livers worldwide, prioritizing patients with HCC, many with compensated cirrhosis, vs those with decompensated cirrhosis, without creating a disparity in access is challenging. Policies continue to evolve. The Model of End Stage Liver Disease (MELD) score prioritizes patients on the LT list. Patients requiring LT for HCC may be underserved on the transplant list by their natural MELD score, as they often do not have underlying decompensated liver disease. Patients with stage T2 lesions, defined as falling within the Milan criteria (Table 1) based upon lesion size and or growth characteristics (on cross-sectional, contrast imaging performed on equipment that meets minimal technical specifications), are eligible for MELD exception points in the US. The scans must be interpreted by a radiologist at a liver transplant centre. If the lesion is atypical, a biopsy must be positive for HCC. Once a patient is listed for LT with a MELD exception, there is a 6-month waiting period for implementation of the exception, partly to decrease the risk of being transplanted too early with an HCC that exhibits aggressive tumour biology resulting in a poorer post-transplant prognosis. The MELD exception points are capped at 34, thus improving access for patients with decompensated cirrhosis with a MELD >34. These changes have increased the waiting times for patients with HCC.

The maximum tumour size and number considered suitable for LT is now extended beyond the Milan criteria. The University of California at San Francisco (UCSF) criteria, published in 2006, (Table 1) have now been adopted across the US. The criteria state that an initial tumour burden of a single lesion ≤6.5 cm or up to 3 lesions, each ≤4.5 cm and with an aggregate diameter ≤8 cm are acceptable for LT. However, to be eligible for the MELD exception, the HCC must be downstaged

Abbreviations: AFP, alpha-fetoprotein; CNI, calcineurin inhibitor; DBD, donation after brain death; DCD, donation after cardiac death; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; LDLT, living donor liver transplantation; LRT, locoregional therapy; LT, liver transplantation; MELD, model of end-stage liver disease; mTOR, mammalian target of rapamycin; MVI, microvascular invasion.
using locoregional therapy (LRT) to within the Milan criteria. Patients transplanted meeting the UCSF criteria and downstaged to the Milan criteria have outcomes similar to those initially within the Milan criteria. Another model for predicting the outcomes of LT is Metroticket 2.0, which predicts 5-year survival and the risk of HCC-related death after LT based upon the sum of viable tumour size in cm plus the number of lesions, and the latest AFP, as well as a model using explant pathology (Table 1). Of note, the model predicts a worse outcome for patients with hepatitis C virus (HCV) infection, but the study was performed in patients transplanted before direct-acting antivirals (DAAs).

Alpha-fetoprotein (AFP) has repeatedly been shown to identify patients with HCC with a high risk of recurrence after LT. Patients with HCC within the Milan Criteria but an AFP >1000 ng/mL have a 5-year recurrence-free survival of only 20%. Thus, these patients must demonstrate an AFP response to LRT to be considered for LT. In a recent analysis of UNOS data evaluating patients undergoing downstaging of HCC, an AFP ≥100 ng/mL was an independent predictor of post-LT HCC recurrence.

Since patients may receive multiple treatments for HCC over an extended period of time, dynamic models could improve prediction of post-LT HCC recurrence. The Hazard Associated with Liver Transplantation for Hepatocellular Carcinoma (HALTHCC) score was developed to predict overall post-LT survival and was recently validated in an international cohort. It uses pre-LT AFP, MELD-sodium, and tumour burden as a continuous risk metric. There was a strong correlation between pre-LT risk and explant pathology predicting recurrence, but further prospective studies are needed to test this score.

3 | MANAGEMENT OF PATIENTS WITH HCC ON THE WAITING LIST

Most patients on the waiting list with HCC will undergo LRT as a bridge to LT. Modalities include trans-arterial chemoembolization, radio-embolization, radiofrequency ablation, microwave ablation, and stereotactic body radiation therapy. LRT prevents wait-list drop-off because of tumour progression. In a propensity matched analysis from the UK, one session of LRT was associated with a 49% lower risk of delisting for progression of HCC and/or post-LT recurrence. This advantage was lost if more than 3 LRTs were needed, which might suggest that poorer tumour biology and/or longer waiting times are risks of a worse outcome. The goal of these bridging therapies is to achieve a complete response, defined by the absence of viable tumour on cross-sectional imaging and AFP <100 ng/mL. Patients with a complete response had the best outcomes in a study evaluating the Modified Response Evaluation Criteria in Solid Tumours (mRECIST) classification immediately following the first LRT.

3.1 | Downstaging to within the Milan criteria

To be eligible for LT and the MELD exception, patients with a tumour burden outside of the Milan criteria must undergo LRT to downstage the tumour burden to within the Milan criteria. Moreover, downstaging may allow time to determine whether the biology of a patient’s HCC is favourable for LT. A multicenter study evaluated 187 consecutive patients with HCC and initial tumours outside the Milan criteria (single lesion ≤8 cm, 2-3 lesions each ≤5 cm or 4-5 each ≤3 cm with an aggregate ≤8 cm), who were enrolled in a downstaging protocol. Successful downstaging to within the Milan criteria followed by LT was achieved in 58% of patients. Tumour progression occurred in 32% of patients and 5% had liver-related deaths without LT. On multivariate analysis, a pretreatment AFP >1000 ng/mL (HR 3.3) and Childs Pugh Class B or C (HR 1.6) were associated with treatment failure, suggesting that these patients were unlikely to benefit from downstaging. In a US analysis of 3819 patients with HCC from 2012-2015 in the UNOS database, the 3-year post-LT HCC recurrence was 6.9% in those within the Milan criteria. 12.8% in those downstaged through UNOS downstaging criteria and 16.7% in those downstaged from beyond the UNOS downstaging criteria. Independent predictors of post-LT deaths in the downstaged groups were an AFP ≥100 at the time of LT (HR 2.4) and being in short (<3 months) or medium wait-time (3-9 months) vs long wait-time (>9 months) regions (HR 3.1), suggesting that wait-time can help define “low-risk” tumour biology.

3.2 | HCC-treatment in patients with viral hepatitis

Concurrent treatment of the underlying liver disease is important, as this can reduce the risk of further liver decompensation and increase the patient’s ability to receive and tolerate LRT. All patients

Key points

- Hepatocellular carcinoma (HCC) is the indication for ~30% of the liver transplants performed in the US and Europe
- Patients with T2 HCC (within Milan criteria) or those downstaged by locoregional therapy to within the Milan criteria are acceptable candidates for liver transplantation.
- Treatment of concurrent chronic viral hepatitis in patients with HCC improves waiting list survival. Direct-acting antivirals for HCV do not increase the risk of recurrent HCC after locoregional therapy.
- Models including the RETREAT and MORAL scores can be used to predict post-liver transplant recurrence of HCC to tailor surveillance and management.
- A multidisciplinary approach to treatment should be considered to optimize outcomes in patients with recurrent HCC after liver transplantation, including surgical resection, locoregional therapy, adjustment of immunosuppression and systemic chemotherapy.
with chronic hepatitis B virus (HBV) infection should be on antiviral therapy, preferably entecavir or tenofovir. Treatment with DAAs can be considered in patients with HCV, although experts suggest waiting until a complete response to LRT has been achieved. Although the rates of a sustained virological response are modestly reduced in patients with HCC compared to those without (~80%), this should not prevent treatment. Transplanting livers from donors who are positive for hepatitis B core antibody, indicating possible prior exposure to HBV, can be safely and successfully done with appropriate post-LT viral prophylaxis. With the introduction and widespread availability of DAA therapy for HCV, livers from HCV-viremic donors are now being used in HCV-uninfected recipients. However, the data are insufficient to determine if these livers will influence post-LT HCC recurrence.

Living donor liver transplantation (LDLT) provides another opportunity to expand donor options in patients with HCC and is particularly valuable in regions where waiting times are long and patients are at risk of delisting because of tumour progression. A multicenter study from France compared the outcomes of patients with cirrhosis and HCC who underwent LDLT (n = 79) and DBD (n = 782). There were no differences in the groups for pre-LT treatment of HCC or tumour burden in the explant exceeding the Milan criteria, but the AFP was higher in the LDLT group. There were no differences in overall intent-to-treat survival at 5 years (73.2% vs 66.7%, respectively) or post-LT HCC recurrence (10.9% vs 11.2% respectively). It is important to note that the delisting rate in the DBD group was 20.7%, mostly because of tumour progression compared to none in the LDLT group. In considering the risk of HCC recurrence, the waiting-time before LDLT is relevant to the risk of HCC recurrence, because short waiting-times may not provide sufficient time for evaluation of tumour biology and response to LRT, which could improve stratification for the risk of post-LT recurrence.

### Table 1: Criteria for transplanting patients with hepatocellular carcinoma

| Criteria | Tumour burden limits | Indicators of poor prognosis | Outcomes |
|----------|----------------------|------------------------------|----------|
| Milan    | 1 lesion ≤ 5 cm or up | AFP > 1000 ng/mL predicts recurrence and poor survival<sup>6</sup> | 4-y overall/recurrence-free survival 85%/92% Recurrence probability at 3 y 6.9% (3) |
| UCSF     | 1 lesion ≤ 6.5 cm | Survival of 90% and 75.2%, at 1 and 5 y, respectively, but 50% 1-year survival if these criteria were exceeded (2). | 5-y survival 80% (5) |
| Metroticket 2.0 | Based upon maximal viable tumour size, plus number of tumours and AFP (3) | |
| UNOS-Downstaging | 1 lesion < 8 cm 2-3 lesions < 5 cm and the aggregate diameter < 8 cm or 4-5 each ≤ 3 cm with an aggregate ≤ 8 cm | Pre-treatment AFP > 1000 ng/mL and/or Childs Pugh Class B or C predict downstaging failure (8) AFP > 100 ng/mL at LT predicts recurrence; Increased risk of post-LT death in short and medium wait time regions (5) | 3-y post-OLT survival 79.1% 3-y recurrence probability 12.8% (5) |

<sup>a</sup>Provides a risk assessment post-LT based upon the sum of viable tumour size in cm plus the number of lesions and the AFP predicts outcomes. http://www.hcc-olt-metroticket.org/#calculator

4 | TRANSPLANT-SPECIFIC CONSIDERATIONS

#### 4.1 | Donor selection in patients with HCC

Timely access to LT can affect LT outcomes in patients with HCC. One study has suggested that to minimize the risk of post-LT recurrence in patients with HCC the optimal waiting time was at least 6 months and no more than 18 months. The use of extended criteria donors is an attractive way to increase access to donors in areas with longer LT waiting-times. Because donor quality can influence graft outcomes, investigators have evaluated whether extended criteria donors and living donors have a different risk of recurrent post-LT HCC.

Donation after cardiac death (DCD) recipients have higher rates of biliary complications and poorer overall survival than donation after brain death (DBD) recipients. However, in the largest single-centre experience examining the impact on HCC recurrence (340 DBD and 57 DCD), there was no difference in recurrence-free survival or recurrence rate of HCC after LT. Transplanting livers from donors who are positive for hepatitis B core antibody, indicating possible prior exposure to HBV, can be safely and successfully done with appropriate post-LT viral prophylaxis. With the introduction and widespread availability of DAA therapy for HCV, livers from HCV-viremic donors are now being used in HCV-uninfected recipients. However, the data are insufficient to determine if these livers will influence post-LT HCC recurrence.
4.2 Immunosuppression and prophylactic systemic chemotherapy

Patients at high risk of recurrent HCC may benefit from adjustment of their post-LT immunosuppression. Immunosuppression has been shown to be involved in accelerated growth of recurrent post-LT HCC. The use of higher levels of calcineurin inhibitors (CNI) earlier in the post-LT phase has been associated with an increased risk of HCC recurrence.16 The mammalian target of rapamycin (mTor) inhibitors, sirolimus and everolimus, has been associated with antineoplastic effects on HCC,17 and their use has been associated with lower HCC recurrence rates compared to CNI.18 In a prospective, randomized, open-label, international trial of 525 LT recipients with HCC, including sirolimus or not as part of the immunosuppression regimen, sirolimus was associated with statistically better recurrence-free survival at year 3 (HR 0.7; CI 95% 0.48-1.00) but not at year 5 (HR 0.84; 95% CI, 0.62-1.15).19 Thus, early adjustment of immunosuppression limiting the use of CNI and using m-TOR inhibitors could help reduce HCC recurrence rates. The outcomes of preemptive sorafenib, a multitargeted, orally active tyrosine kinase inhibitor, in LT recipients at high risk of HCC recurrence have been mixed,20,21 and systemic chemotherapy is not routinely recommended to prevent recurrent HCC, even in high-risk patients.

5 HCC recurrence after liver transplantation

HCC recurrence occurs despite careful selection of LT recipients and is because of tumour cell dissemination from circulating cancer cells and micrometastases before or during total hepatectomy.22 HCC recurrence usually occurs early, a median of 12.3 months after LT. Late recurrence more than 2 years after LT is rare.23 Recurrent HCC developed in 29 of a series of 132 LT patients for HCC in Italy (15.9%). Fifteen (71%) of these occurred within the first 18 months, and only 2 (7%) more than 2 years later.23 The most common sites of HCC recurrence in a study of 84 cases of recurrent HCC were the lung (44.0%), bone (29.8%), liver (26.2%) and peritoneum (26.2%).24

Overall, HCC recurs in about 10%-15% of LT recipients.20,25 Several factors have been associated with post-LT recurrence. Microvascular invasion (MVI) on the explant has been associated with increased HCC recurrence and decreased survival.21 There is an approximately 3.8- to 4.9-fold increase in HCC recurrence with MVI.24 Pre-LT assessment of MVI and tumour grade has been limited by the poor accuracy of preoperative biopsy, which often does not correlate with the grade or presence of microvascular invasion on the final pathology report. Recent efforts have been made to non-invasively predict explant microvascular invasion through radiogenomics. Radiogenomics maps the imaging features of the tumour to corresponding gene expression profiles to determine the genetic characteristics of the tumour. Certain features of HCC on CT have been discovered through radiogenomics, including the presence of internal arteries in the tumour and hypodense halos around the tumour. Radiological features are promising for the prediction of microvascular invasion in the resected liver.27 Further prospective studies are needed to determine the validity of this growing field to predict outcomes.

Elevated AFP levels are increasingly recognized as a sign of worse tumour biology and increased HCC recurrence after LT.25 The number of tumours, higher tumour grade, shorter waiting time before LT, and poor response to LRT have all been found to be predictive of higher HCC recurrence rates after LT.28-31

Several models have been developed to predict HCC recurrence after LT. The Risk Estimation of Tumour Recurrence After Transplant (RETREAT) score was developed through a multicenter study to risk-stratify HCC recurrence after LT. The study showed that in multivariate analysis, elevated AFP, the presence of MVI on the explant, and the largest viable tumour diameter plus the number of viable tumours on the explant was predictive of HCC recurrence. The RETREAT score was developed with these factors and assigning 0-3 points for increasing AFP levels, 2 points for the presence of MVI, and 0-3 points for the increasing size of the largest viable tumour diameter plus the number of viable tumours for a total score of 8 (Table 2). A RETREAT score of 0 is predictive of a 1- and 5-year recurrence risk of only 1.0% (95% CI, 0.0%-2.1%) while a score of 5 or higher predicted 1-year and 5-year recurrence rates of 39.3% (95% CI, 25.5%-50.5%) and 75.2% (95% CI, 56.7%-85.8%) respectively. The score performed well in the validation cohort of the study with a c-statistic of 0.82 (95% CI, 0.77-0.86), and using the net reclassification index, the score outperformed the Milan criteria at predicting HCC recurrence 1 year (0.40, P = .01) and 5 years after LT (0.31, P < .01).24

The Model of Recurrence After Liver Transplantation (MORAL) developed by investigators at Columbia University incorporates the pre-LT neutrophil-lymphocyte ratio (NLR) to its prediction model. A pre-LT NLR ≥5 has been shown to predict poor outcomes in HCC.31 The pre-MORAL score includes a combination of pre-LT NLR ≥5, AFP >200 ng/mL, and largest tumour size >3 cm (pre-LT values). The post-MORAL score (post-LT findings) includes the presence of grade 4 tumour, vascular invasion, largest tumour size >3 cm and >3 tumours on the explant. The resulting combined, combo-MORAL score was found to have a c-statistic of 0.91 (95% CI, 0.87-0.95) with a better performance than the Milan criteria (0.63; 95%, 0.54-0.71) and UCSF criteria (0.57; 95% 0.47-0.66).26 Further multicenter studies are needed to confirm the validity of these findings.

Accurate models to predict HCC recurrence can help tailor surveillance after LT. High risk patients can undergo more frequent surveillance imaging while low risk patients may be able to reduce or even avoid unnecessary surveillance imaging after LT. While there are no standard guidelines for post-LT HCC surveillance, the authors of the RETREAT study propose more frequent HCC surveillance for RETREAT scores of ≥5, consisting of multiphasic, cross-sectional imaging of the abdomen as well as CT of the chest and AFP every 3-4 months for 2 years, then every 6 months from years 2-5. The authors recommend surveillance every 6 months for 2 years for a score of 1-3 and every 6 months for 5 years for a score of 4. They do not recommend surveillance in patients with a RETREAT score of 0 because of the low risk of HCC recurrence in this group (1.0%; CI 95%, 0.0%-2.1%) at 5 years (Table 3).24
of localized recurrent HCC (42 months) and sorafenib use (18 months) were associated with higher survival rates, although, sorafenib use was associated with increased adverse effects.35 The best supportive care was associated with the lowest survival rate (3.3 months).35 If feasible, resection or LRT should be attempted in combination with the use of sorafenib and mTOR inhibitors as any form of therapy appears to have better overall outcomes than supportive care.

The use of checkpoint inhibitor immunotherapy has increased for the treatment of HCC with promising results as second-line therapy for HCC if sorafenib fails.36 At the time of this writing, 2 checkpoint inhibitors, nivolumab and pembrolizumab, have been approved for the treatment of HCC by the US Food and Drug Administration. Both are anti-PD1 monoclonal antibodies that release the "brakes" of the immune system to control HCC. Although pre-LT treatment data have been promising for HCC, no current data exists to show a benefit for post-LT HCC recurrence. In fact, the use of checkpoint immunotherapy must be carefully considered because of potential uncontrolled immune reactivation. Several case reports of severe acute T-cell-mediated rejection and antibody-mediated rejection have been described in the post-LT setting with graft loss and death.37 Further efficacy and safety studies are needed before routine use of these medications.

TABLE 2 RETREAT Score

| Risk factor                              | RETREAT points |
|-----------------------------------------|----------------|
| 1. AFP at LT, ng/mL                     |                |
| 0-20                                    | 0              |
| 21-99                                   | 1              |
| 100-999                                 | 2              |
| ≥1000                                   | 3              |
| 2. Microvascular invasion               | 2              |
| 3. Largest viable tumour diameter (cm)  |                |
| plus number of viable tumours           |                |
| 0                                       | 0              |
| 1.1-4.9                                 | 1              |
| 5.0-9.9                                 | 2              |
| ≥10                                     | 3              |

*The RETREAT score ranges from 0-8 and is calculated from the sum of the 3 risk factor points.

Adapted from Mehta N, et al. Validation of a risk estimation of tumour recurrence after transplant (RETREAT) score for hepatocellular carcinoma recurrence after liver transplant. JAMA Oncol. 2017;3:493-500.

TABLE 3 Proposed HCC surveillance schedule after LT based on RETREAT score

| RETREAT score | Surveillance schedule |
|---------------|-----------------------|
| 0             | No surveillance       |
| 1-3           | Every 6 mo for 2 y    |
| 4             | Every 6 mo for 5 y    |
| ≥5            | Every 3-4 mo for 2 y, followed by every 6 mo from years 2 through 5 |

*Recommended surveillance consists of cross-sectional, multiphase imaging (CT or MRI) of abdomen along with chest CT and AFP.

Adapted from Mehta N, et al. Validation of a risk estimation of tumour recurrence after transplant (RETREAT) score for hepatocellular carcinoma recurrence after liver transplant. JAMA Oncol. 2017;3:493-500.

5.1 Treatment of recurrent HCC after liver transplantation

Overall survival if recurrent HCC is detected after LT is poor. Multifocal recurrence and early recurrence after LT (≤6 months) are associated with worsened survival.32,33 At present there is no consensus algorithm for the treatment of recurrent HCC. An earlier diagnosis of recurrence could help improve outcomes as several case series have shown improved survival in patients who underwent resection for localized recurrence compared to patients with multifocal recurrence.23,32,33 Early use of sorafenib and other mTOR inhibitors may also be options as well as resection or LRT, though more data are needed.34 In a metaanalysis of 1021 LT recipients with HCC recurrence, the median survival after diagnosis of recurrence was 13 months. A variety of treatments were used including surgical resection, systemic therapy with sorafenib, LRT, and the best supportive care. Surgical resection

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6 | CONCLUSION

Liver transplantation is effective therapy in patients with HCC within the Milan criteria or in those who can be downstaged to within the Milan criteria. Expansion of eligibility criteria is being explored to identify the upper limits of tumour burden that can be effectively managed with LT. However, the limitations of access to donor organs prevent large numbers of patients from having LT as definitive treatment. Thus, expanding donor options, including living donor LT, is important. Outcomes for LT with recurrent HCC are poor, but are improved by early detection, highlighting the importance of surveillance in "at-risk" recipients. To improve the outcomes of patients with post-LT HCC recurrence, a multidisciplinary approach to treatment should be considered including surgical resection, locoregional therapy, adjustment of immunosuppression and systemic chemotherapy.

CONFLICT OF INTEREST

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