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Liver Transplantation Outcomes in a U.S. Multicenter Cohort of 789 Patients With Hepatocellular Carcinoma Presenting Beyond Milan Criteria

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BACKGROUND AND AIMS: The Organ Procurement and Transplantation Network recently approved liver transplant (LT) prioritization for patients with hepatocellular carcinoma (HCC) beyond Milan Criteria (MC) who are down-staged (DS) with locoregional therapy (LRT). We evaluated post-LT outcomes, predictors of down-staging, and the impact of LRT in patients with beyond-MC HCC from the U.S. Multicenter HCC Transplant Consortium (20 centers, 2002-2013).

APPROACH AND RESULTS: Clinicopathologic characteristics, overall survival (OS), recurrence-free survival (RFS), and HCC recurrence (HCC-R) were compared between patients within MC (n = 3,570) and beyond MC (n = 789) who were down-staged (DS, n = 465), treated with LRT and not down-staged (LRT-NoDS, n = 242), or untreated (NoLRT-NoDS, n = 82). Five-year post-LT OS and RFS was higher in MC (71.3% and 68.2%) compared with DS (64.3% and 59.5%) and was lowest in NoDS (n = 324; 60.2% and 53.8%; overall $P < 0.001$). DS patients had superior RFS (60% vs. 54%, $P = 0.043$) and lower 5-year HCC-R (18% vs. 32%, $P < 0.001$) compared with NoDS, with further stratification by maximum radiologic tumor diameter (5-year HCC-R of 15.5% in DS/<5 cm and 39.1% in NoDS/>5 cm, $P < 0.001$). Multivariate predictors of down-staging included alpha-fetoprotein response to LRT, pathologic tumor number and size, and wait time >12 months. LRT-NoDS had greater HCC-R compared with NoLRT-NoDS (34.1% vs. 26.1%, $P < 0.001$), even after controlling for clinicopathologic variables (hazard ratio [HR] = 2.33, $P < 0.001$) and inverse probability of treatment-weighted propensity matching (HR = 1.82, $P < 0.001$).

CONCLUSIONS: In LT recipients with HCC presenting beyond MC, successful down-staging is predicted by wait time, alpha-fetoprotein response to LRT, and tumor burden and results in excellent post-LT outcomes, justifying expansion of LT criteria. In LRT-NoDS patients, higher HCC-R compared with NoLRT-NoDS cannot be explained by clinicopathologic differences, suggesting a potentially aggravating role of LRT in patients with poor tumor biology that warrants further investigation. (Hepatology 2020;72:2014-2028).

Liver transplantation (LT) remains the gold standard curative treatment for eligible patients with unresectable hepatocellular

Abbreviations: AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer; CI, confidence interval; DS, down-staged; HCC, hepatocellular carcinoma; IQR, interquartile range; IPTW, inverse probability of treatment weighting; LRT, locoregional therapy; LT, liver transplantation; MC, Milan Criteria; MELD, Model for End-Stage Liver Disease; NET, neutrophil extracellular traps; NLR, neutrophil-to-lymphocyte ratio; NoDS, not down-staged; OPTN, Organ Procurement and Transplantation Network; OR, odds ratio; OS, overall survival; RFS, recurrence-free survival; TACE, transarterial chemoembolization; UMHTC, United States Multicenter HCC Transplant Consortium; UNOS, United Network for Organ Sharing.

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carcinoma (HCC)[1] and limited tumor burden. Since 1996, the Milan Criteria (MC) have been widely adopted to select patients who are most likely to achieve excellent post-LT outcomes.[1] With Model for End-Stage Liver Disease (MELD) exception point prioritization based on these criteria, patients with HCC within MC have 5-year post-LT survival rates of 75%-80%[2,3] and HCC recurrence rates of 10%-15%.[1,4,5] However, with rising HCC incidence[6] and mortality[7] in the United States, the demand for LT as a potential curative treatment has also increased.

In recent years, significant efforts have been made by the transplant community to expand selection criteria to include dynamic markers of tumor biology with the goal of maximizing "transplant benefit" for patients with HCC presenting beyond MC. Tumor down-staging, defined as the reduction of viable tumor size to acceptable LT criteria using pretransplant locoregional therapy (LRT), uses radiographic response to LRT as a prognostic marker to select patients beyond MC who will likely have excellent post-LT outcomes.[8] In 2017, the Organ Procurement and Transplantation Network (OPTN) expanded inclusion criteria to allow prioritization of HCC candidates presenting with tumors modestly beyond MC who are successfully down-staged to within MC.[9]

Fueling these policy changes are several single-center studies showing comparable post-LT outcomes in expanded-criteria patients who were successfully down-staged compared to patients initially within MC.[10-14] Recently, a multicenter evaluation of 109 patients at three transplant centers in region 5 who underwent LT after successful down-staging showed excellent post-LT mortality and HCC recurrence rates, with 5-year recurrence-free survival estimated at 87%.[13] A limitation of this study was the long median wait-list times of 13 months observed after down-staging, and 18% wait-list

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dropout rate of down-staged patients, suggesting that the individuals who made it to transplant were a select group with more favorable tumor biology and likely superior post-LT outcomes. The generalizability of these findings to other regions is unclear, and studies of down-staging in regions with varying wait-list times are still needed.

In the largest multicenter study to date using our national consortium of 789 patients presenting with tumors beyond Milan Criteria (MC) undergoing LT across 10 of 11 United Network for Organ Sharing (UNOS) regions, we sought to evaluate long-term post-LT outcomes and assess the impact of LRT on post-LT HCC recurrence and survival. We also aimed to identify factors associated with successful down-staging, which may help to define a tumor's biology and guide pre-LT LRT strategies.

Methods

The U.S. Multicenter HCC Transplant Consortium (UMHTC) is a retrospective database initiated in January 2015 of patients with HCC undergoing LT. It encompasses 20 academic transplant centers comprising 10 UNOS regions (Supporting Fig. S1). The consortium includes adults aged 18 years or older with HCC who underwent LT from 2002 to 2013 regardless of tumor size, requirement for MELD exception points, follow-up time, or non–HCC-related death. HCC was diagnosed by pretransplant radiographic imaging using OPTN 5 criteria, biopsy, or incidental discovery on explant pathology. Patients who had cholangiocarcinoma, mixed hepatocellular cholangiocarcinoma, fibrolamellar HCC, or hepatoblastoma were excluded. The study was approved by institutional review boards at each transplant center, and data were collected, deidentified, and stored in a password-encrypted central database at the University of California, Los Angeles.

The primary objective of this study was to examine post-LT outcomes, including HCC recurrence and survival, and the impact of pretransplant LRT on the rate of successful down-staging in LT patients presenting with beyond-MC tumors. LT recipients transplanted within the study period whose tumors were radiographically within MC (1 lesion ≤5 cm, up to 3 lesions ≤3 cm each), regardless of their explant pathologic findings, were used as the comparison group. Overall and recurrence-free survival were compared between patients who presented within MC, beyond MC but were down-staged with LRT (DS), and beyond MC but were not down-staged (NoDS). NoDS patients were further stratified by whether they received LRT (LRT-NoDS) or not (NoLRT-NoDS). Successful down-staging was defined as reduction in viable tumor burden using LRT to a residual size and diameter within MC as evaluated on contrast-enhanced radiologic examination prior to LT.[8]

Patient variables included age, sex, etiology of liver disease, laboratory and transplant match MELD scores, time from listing to LT, and pretransplant neutrophil-to-lymphocyte ratio (NLR). Tumor- and treatment-related variables included radiologic maximum tumor diameter, maximum and immediate pretransplant serum alpha-fetoprotein (AFP), receipt of LRT, number and modality of LRTs, and AFP response to LRT. LRT modality was categorized into transarterial chemoembolization (TACE) without ablation, ablation without TACE, both TACE and ablation, and other (including transarterial radioembolization with Yttrium^{90}, percutaneous ethanol ablation, surgical resection, cryoablation, and radiation-based therapies). Explant pathologic variables were reported by each transplant center using a standardized spreadsheet and included total tumor number, maximum tumor diameter, grade/differentiation, presence of micro- and macrovascular invasion, and American Joint Committee on Cancer (AJCC) tumor staging. Tumor grade/differentiation was categorized based on the worst features present in any nodule in the entire specimen and in accordance with the College of American Pathologists HCC cancer protocol synopsis[15] (grade 1 = well, grade 2 = moderate, and grade 3 = poor). Patient-specific follow-up time was calculated from the date of LT to post-LT HCC recurrence or death, with all LT recipients characterized as alive without recurrence, alive with recurrence, dead due to recurrence, or dead not related to HCC recurrence at time of last follow-up.

STATISTICAL ANALYSIS

Categorical variables were compared using chi-squared or Fisher's exact test and reported as percentages and frequencies. Continuous variables

were compared using the Wilcoxon rank-sum test or Student *t* test and reported as means and standard deviations or medians and interquartile ranges (IQRs). Covariates were compared among MC, DS, and NoDS groups. Further comparisons were made between DS and LRT-NoDS groups and between LRT-NoDS and NoLRT-NoDS groups. The Kaplan-Meier method was used to construct overall survival (OS) and recurrence-free survival (RFS) curves, and curves across specific groups were compared using the log-rank test. Cumulative incidence curves of recurrence were compared across specific groups using the Gray's test and accounted for the competing risk of non–HCC-related death.

Logistic regression was used to identify predictors of successful down-staging in patients undergoing LRT, with and without adjustment for pre-LT factors, explant characteristics, and individual wait times. Additionally, competing risk Fine and Gray regression model was used to identify factors associated with time to post-LT HCC recurrence, accounting for the competing risk of non–HCC-related death, in patients presenting beyond MC subcategorized by down-staging status. The variables for immediate pretransplant AFP, NLR, and pathologic maximum tumor diameter were log-transformed as those values approximated a normal distribution compared with a skewed distribution on the original scale. Backward stepwise regression was used with a *P* value <0.25 as the retention criterion for the final models, and associations were reported as odds ratios (ORs) for the logistic regression and hazard ratios (HRs) for the Fine and Gray regression, along with 95% confidence intervals (CIs). All statistical tests were two-sided and a *P* value of 0.05 or less was considered statistically significant.

To account for a patient's probability of receiving LRT that could lead to selection bias, inverse probability of treatment weighting (IPTW) multivariable regression was also performed in the subset of patients not successfully down-staged. The propensity score was the probability of receiving LRT after conditioning on other pre- and post-LT covariates. Each patient was assigned a weight corresponding to the inverse of the propensity score under the logistic model. Propensity scores were compared in treated and untreated patients to confirm that propensity matching successfully balanced the two groups. An IPTW competing risk Cox regression model was then performed and estimates were reported as hazard ratios and 95% CIs. Missing values were imputed using the Markov Chain Monte Carlo method. Linearity was confirmed by fitting splines. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

During the study period, 4,359 patients in the UMHTC with a known pre-LT diagnosis of HCC underwent LT, with 3,570 patients presenting within MC and 789 patients with beyond-MC tumors. Of these 789 patients with HCC beyond MC, 465 (58.9%) patients received LRT and were down-staged to MC prior to LT (DS), 242 (30.7%) received LRT and were not down-staged (LRT-NoDS), and 82 (10.4%) patients were not down-staged and did not receive pre-LT LRT (NoDS-NoLRT). In LT recipients presenting beyond MC, 454 (57.5%) patients were alive without HCC recurrence, 183 (23.2%) had HCC recurrence, of whom 32 were alive and 151 had died, and 152 had died not due to HCC recurrence at a median follow-up time of 43.9 months [IQR: 23.0-76.9]. Median time to recurrence was 13.6 months [7.6-29.9].

COMPARISON OF ALL BEYOND-MC PATIENTS BY DOWN-STAGING STATUS

Baseline demographic, laboratory, locoregional treatment, and explant pathologic characteristics of the cohort, stratified by down-staging and LRT status, are shown in Table 1. Compared with No-DS, DS patients were older (59 [54-64] vs. 58 [53-63] years, $P = 0.047$) and had longer median wait time (134 [45-263] vs. 81 [29-202] days, $P < 0.001$), lower median laboratory MELD (11 [8-14] vs. 12 [9-17], $P = 0.045$) and greater transplant match MELD (23 [22-27] vs. 22 [14-25], $P < 0.001$), lower immediate pre-LT AFP (11 [5-49] vs. 24 [8-109], $P < 0.001$), and better AFP response to LRT (17% vs. 10% with AFP normalization after LRT, $P = 0.002$). In terms of explant characteristics, DS patients were more likely to have fewer tumors (35% vs. 21% with only 1 tumor, 13% vs. 20% with >5 tumors; $P < 0.001$), smaller median maximum tumor diameters (3.5 [2.5-4.5] vs. 4.2 [2.8-5.5] cm, $P < 0.001$), fewer

TABLE 1. Comparison of Characteristics Among 789 HCC Liver Transplant Recipients Outside Milan by Down-Staging Status

	DS (n = 465)	NoDS (n = 324)	*P* Value
Demographics			
Age, median (IQR)	59 (54-64)	58 (53-63)	0.047
Male, %	386 (83)	281 (87)	0.155
Diagnosis, %			
HCV	271 (58)	179 (55)	0.241
NASH	32 (6.9)	19 (5.9)	
Alcohol	46 (9.9)	43 (13)	
HBV	70 (15)	40 (12)	
Other	46 (9.9)	43 (13)	
Median wait list time (days)	134 (45-263)	81 (29-202)	<0.001
Laboratory parameters, median (IQR)			
Laboratory MELD	11 (8-14)	12 (9-17)	0.045
Transplant Match MELD	23 (22-27)	22 (14-25)	<0.001
Pre-LT maximum AFP, ng/mL	28 (9-169)	34 (10-221)	0.104
Immediate pre-LT AFP, ng/mL	11 (5-49)	24 (8-109)	<0.001
AFP response to LRT, n (%)			0.002
Pre-LT AFP = maximum AFP, but ≤20	201 (47)	91 (39)	
Pre-LT AFP < maximum AFP, normalized to ≤20	71 (17)	24 (10)	
Pre-LT AFP < maximum AFP; improved, but not normalized (>20)	87 (20)	58 (25)	
Pre-LT AFP = maximum AFP, no change and >20	71 (17)	61 (26)	
Neutrophil-to-lymphocyte ratio	2.88 (1.88-4.82)	3.00 (1.94-5.01)	0.400
Treatment characteristics, n (%)			
LRT modality			0.732
TACE without thermal ablation	332 (71)	177 (73)	
Thermal ablation without TACE	38 (8)	19 (8)	
TACE and thermal ablation	63 (14)	26 (11)	
Other	32 (7)	19 (8)	
Number of treatments			
1	209 (45)	128 (53)	0.105
2	142 (31)	66 (27)	
3+	114 (25)	47 (20)	
Explant pathology			
Number of tumors, n (%)			<0.001
1	157 (35)	66 (21)	
2	108 (24)	84 (26)	
3	63 (14)	51 (16)	
4	35 (8)	35 (11)	
≥5	82 (19)	85 (27)	
Maximum diameter in cm, median (IQR)	3.5 (2.5-4.5)	4.2 (2.8-5.5)	<0.001
Differentiation, %			
1 - Well	79 (17)	74 (25)	<0.001
2 - Moderate	226 (50)	178 (60)	
3- Poor	52 (11)	45 (15)	
4 - Necrotic/no viable tumor	96 (21)	1 (0.34)	
Vascular invasion, %			<0.001
None	338 (73)	186 (58)	
Microvascular	92 (20)	94 (29)	
Macrovascular	30 (7)	41 (13)	
AJCC T stage, %			<0.001
T1	144 (31)	45 (14)	

TABLE 1. *Continued*

	DS (n = 465)	NoDS (n = 324)	*P* Value
T2	236 (51)	165 (51)	
T3a	51 (11)	68 (21)	
T3b/T4	29 (6)	43 (13)	

Abbreviations: AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer; cPR, complete pathologic response; DS, down-staged; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; NoDS, non–down-staged; TACE, transarterial chemoembolization; UNOS, United Network for Organ Sharing.

poorly differentiated tumors (11% vs. 15%) and greater complete pathologic response with no viable tumor (21% vs. 0.34%, $P < 0.001$), and significantly less microvascular (20% vs. 29%) and macrovascular (7% vs. 13%) invasion ($P < 0.001$) compared with NoDS patients. There were no significant differences in sex, underlying diagnosis, pre-LT maximum AFP, or LRT number or modality, with the majority of patients receiving one LRT (DS 45% vs. NoDS 53%, $P = 0.105$), most commonly TACE without thermal ablation (DS 71.4% vs. NoDS 73.4%, $P = 0.732$).

COMPARISON OF PATIENTS RECEIVING LRT STRATIFIED BY DOWN-STAGING STATUS

Comparison of characteristics among beyond-MC patients receiving LRT and stratified by DS status is shown in Supporting Table S1. Compared with DS, LRT-NoDS patients had lower median transplant match MELD (22 [14-24] vs. 23 [22-27], $P < 0.001$), higher immediate pre-LT AFP (22 [7.5-87] vs. 11.0 [5.0-49], $P < 0.001$), and worse AFP response to LRT (10% vs. 17% with AFP normalization, 26% vs. 17% with no decrease in AFP, $P = 0.002$). Regarding explant pathologic characteristics, LRT-NoDS patients were more likely to have a greater number of tumors (25.4% vs. 18.4% with ≥5 tumors, $P = 0.002$), greater median maximum tumor diameter (4.1 [3.0-5.5] vs. 3.5 [2.5-4.5], $P < 0.001$), more poorly differentiated tumors (16.0% vs. 11.5%, $P < 0.001$), greater microvascular (30.0% vs. 20.0%) and macrovascular (9.2% vs. 6.5%) invasion ($P = 0.003$), and higher T stage ($P < 0.001$) compared with DS patients. There were no significant differences in age, sex, underlying diagnosis, laboratory MELD, pre-LT maximum AFP, NLR, or the number and type of LRT.

COMPARISON OF NON–DOWN-STAGED PATIENTS STRATIFIED BY RECEIPT OF LRT

Comparison of characteristics of the NoDS subset stratified by receipt of LRT is shown in Supporting Table S2. Of 324 NoDS patients, 242 (74.7%) received pre-LT LRT (LRT-NoDS) whereas 82 (25.3%) underwent LT without any prior LRT (NoLRT-NoDS). LRT-NoDS patients had lower median laboratory MELD scores (11 [8-15] vs. 15 [9-23], $P = 0.001$), lower rates of macrovascular invasion (9.2% vs. 23.5%, $P = 0.004$), and fewer advanced-stage tumors (T3a: 20.0% vs. 24.7%; T3b/T4: 10.0% vs. 23.5%, overall $P = 0.006$) compared with NoLRT-NoDS. There were no significant differences in age, median transplant match MELD score, maximum pre-LT AFP, maximum pathologic or radiologic tumor diameter, grade/differentiation, or tumor number.

UNIVARIATE AND MULTIVARIATE ANALYSIS OF PREDICTORS OF SUCCESSFUL DOWN-STAGING

Univariate and multivariate predictors of successful down-staging are shown in Table 2. Significant univariate predictors of down-staging included favorable AFP response to LRT (PreLT AFP < maximum AFP and normalized < 20 [OR = 2.56, CI 1.48-4.45, $P = 0.001$], pre-LT AFP always <20 [OR = 1.83, CI 1.20-2.78, $P = 0.005$), lower AJCC T stage (T1 vs. T3b/T4 [OR = 3.35, CI 1.73-6.49; $P < 0.001$], and wait time >12 months (OR = 2.28, CI 1.31-3.96; $P = 0.003$), whereas presence of microvascular invasion (OR = 0.55; CI 0.38-0.79, $P = 0.001$), increasing pathologic tumor number (any tumor number >1, all $P < 0.05$), and increasing pathologic median maximum tumor diameter (OR = 0.68 per 50% increase, CI

TABLE 2. Univariate and Multivariate Analysis of Predictors of Successful Down-Staging in Patients With HCC Beyond Milan Criteria Undergoing LRT

	Univariate Analysis			Multivariate Analysis		
Variable	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Pretransplant factors						
Maximum radiologic tumor diameter ≥5 cm (vs. <5 cm)	1.02	0.74-1.41	0.901			
Modality of LRT						
TACE	1.00	Reference	N/A			
Thermal ablation	1.11	0.62-2.01	0.725			
TACE and thermal ablation	1.23	0.76-2.00	0.406			
Other	0.76	0.41-1.43	0.393			
Number of pre-LT LRT						
1	1.00	Reference	N/A			
2	1.29	0.89-1.86	0.174			
3+	1.47	0.98-2.21	0.061			
AFP response to LRT						
Pre-LT AFP = maximum AFP, no change and >20	1.00	Reference	N/A	1.00	Reference	N/A
Pre-LT AFP < maximum AFP; improved, but not normalized (>20)	1.40	0.88-2.22	0.157	1.14	0.69-1.87	0.609
Pre-LT AFP < maximum AFP, normalized to ≤20	2.56	1.48-4.45	0.001	1.83	1.01-3.32	0.045
Pre-LT AFP = maximum AFP, but ≤20	1.83	1.20-2.78	0.005	1.56	1.00-2.45	0.052
Explant factors						
Pathologic differentiation						
Well	0.94	0.55-1.59	0.805			
Moderate	1.18	0.80-1.76	0.402			
Poor	1.00	Reference	N/A			
Vascular invasion						
None	1.00	Reference	N/A			
Microvascular	0.55	0.38-0.79	0.001			
Macrovascular	0.61	0.34-1.11	0.105			
Pathologic tumor number						
1	1.00	Reference	N/A	1.00	Reference	N/A
2	0.47	0.31-0.73	0.001	0.51	0.32-0.82	0.005
3	0.50	0.30-0.84	0.008	0.56	0.33-0.96	0.036
4	0.43	0.24-0.79	0.006	0.43	0.23-0.81	0.009
≥5	0.41	0.26-0.64	<0.001	0.40	0.24-0.65	<0.001
Pathologic maximum tumor diameter (per 50% increase)	0.68	0.58-0.79	<0.001	0.63	0.53-0.75	<0.001
AJCC T stage, %						
T1	3.35	1.73-6.49	<0.001			
T2	1.39	0.77-2.50	0.269			
T3a	0.84	0.43-1.65	0.619			
T3b/T4	1.00	Reference	N/A			
Wait time (in months)						
<6	1.00	Reference	N/A	1.00	Reference	N/A
6-9	1.16	0.72-1.89	0.546	1.11	0.67-1.84	0.692
9-12	1.58	0.75-3.32	0.230	1.16	0.53-2.55	0.712
>12	2.28	1.31-3.96	0.003	1.89	1.06-3.36	0.030

Abbreviations: AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer; HCC, hepatocellular carcinoma; LRT, locoregional therapy; LT, liver transplant; TACE, transarterial chemoembolization.

0.58-0.79, $P < 0.001$) were associated with lower likelihood of successful DS. Maximum radiologic tumor diameter, modality or number of pre-LT LRTs, and pathologic grade/differentiation were not associated with successful down-staging in univariate models.

In multivariate analysis, independent predictors of successful DS included normalization of AFP < 20 prior to LT (OR = 1.83, CI 1.01-3.32; $P = 0.045$), wait time >12 months (OR = 1.89, CI 1.06-3.36; $P = 0.030$), pathologic tumor number (all $P < 0.05$ for any tumor number >1), and pathologic maximum tumor diameter (OR = 0.63 per 50% increase, CI 0.53-0.75; $P < 0.001$). To assess whether degree of AFP response impacted down-staging success, we performed additional analyses evaluating complete versus partial normalization of AFP. We found that partial AFP response without normalization of AFP was not associated with down-staging success (data not shown).

SURVIVAL OUTCOMES AND HCC RECURRENCE

At 1, 3, and 5 years after LT, patients within MC had the highest overall (89.9%, 79.5%, 71.3%; Fig. 1A) and recurrence-free survival (87.6%, 76.2%, 68.2%; Fig. 1B) and lowest incidence of HCC recurrence (3.9%, 8.8%, and 11.1%; Fig. 1C) whereas NoDS patients had the lowest overall (90.3%, 72.0%, 60.2%, $P < 0.001$; Fig. 1A) and recurrence-free survival (79.7%, 63.1%, 53.8%, $P < 0.001$; Fig. 1B) and highest post-LT HCC recurrence (14.7%, 27.1%, 32.1%; $P < 0.001$; Fig. 1C). DS patients had 1-, 3-, and 5-year overall survival (89.6%, 75.2%, 64.3%) inferior to MC ($P = 0.039$) and nonsignificantly greater than NoDS patients ($P = 0.108$; Fig. 1A), recurrence-free survival (85.0%, 69.5%, 59.5%) inferior to MC ($P = 0.006$) but superior to NoDS patients ($P = 0.043$; Fig. 1B), and post-LT HCC recurrence (7.6%, 15.1%, and 18.7%) greater than MC ($P < 0.001$) but significantly lower than NoDS patients ($P < 0.001$; Fig. 1C).

When further stratifying the 789 beyond MC by DS status and receipt of LRT, LRT-NoDS patients had similar 1-, 3-, and 5-year overall (90.8%, 72.0%, 59.7% vs. 89.0%, 71.5%, 61.2%, $P = 0.942$; Fig. 2A) and recurrence-free survival (78.7%, 61.9%, 52.9% vs. 82.8%, 66.5%, 56.3%, $P = 0.527$; Fig. 2B) compared with NoLRT-NoDS patients. Interestingly, recipients who received LRT and were not successfully down-staged (LRT-NoDS) had an increased 1-, 3-, and 5-year risk of recurrence compared with NoDS patients not receiving LRT at all (16.7%, 30.4%, 34.1% vs. 8.6%, 18.7%, 26.1%, $P < 0.001$; Fig. 2C). Additional subgroup analysis was performed to evaluate the impact of maximum radiologic tumor diameter on post-LT HCC recurrence (Fig. 3). DS patients with maximal tumor diameter ≤5 cm had the lowest incidence of HCC recurrence at 5 years (15.5%, HR 1.00, reference), whereas NoDS patients with maximal tumor diameter >5 cm had the highest 5-year HCC recurrence incidence (39.1%, HR 3.11, $P < 0.001$). NoDS patients with a maximal tumor diameter ≤5 cm had a 5-year HCC recurrence incidence of 27.9% (HR 1.95, $P = 0.001$ compared with DS rad max ≤5 cm), significantly lower compared with NoDS patients with tumors >5 cm (39.1%, $P = 0.020$), but only slightly higher recurrence compared with DS patients with maximal tumor diameter >5 cm (23.6%, $P = 0.368$ compared with NoDS, rad max ≤5 cm; HR 1.61, $P = 0.039$ compared with DS, rad max ≤5 cm).

MULTIVARIATE RISK FACTORS FOR HCC RECURRENCE IN NON–DOWN-STAGED PATIENTS BEYOND MC

Despite a greater incidence of macrovascular invasion (23.5% vs. 9.2%, $P = 0.004$) and advanced pathologic tumor stage (23.5% vs. 10.0% T3b/T4, $P = 0.006$; Supporting Table S2), NoLRT-NoDS patients had a significantly lower incidence of HCC recurrence compared with LRT-NoDS patients. To investigate this unexpected result, we performed a multivariate competing risk regression analysis to identify predictors of HCC recurrence in NoDS patients (Table 3). Significant independent predictors of HCC recurrence included hepatitis C virus cirrhosis (HR = 0.55, CI 0.31-0.95; $P = 0.033$), pre-LT NLR (HR = 2.06 per log unit increase, CI 1.29-3.30, $P = 0.003$), immediate pretransplant log AFP (HR = 1.07 per 50% increase, CI 1.02-1.12; $P = 0.008$), microvascular invasion (HR = 2.31, CI 1.45-3.67; $P < 0.001$), macrovascular invasion (HR = 2.54, CI 1.36-4.76; $P = 0.004$), and moderate (HR = 4.64, CI 1.88-11.46; $P < 0.001$) and poor differentiation (HR = 5.42, CI 1.91-15.42; $P = 0.002$). Notably, wait time was not predictive of post-LT HCC recurrence in non–down-staged LT

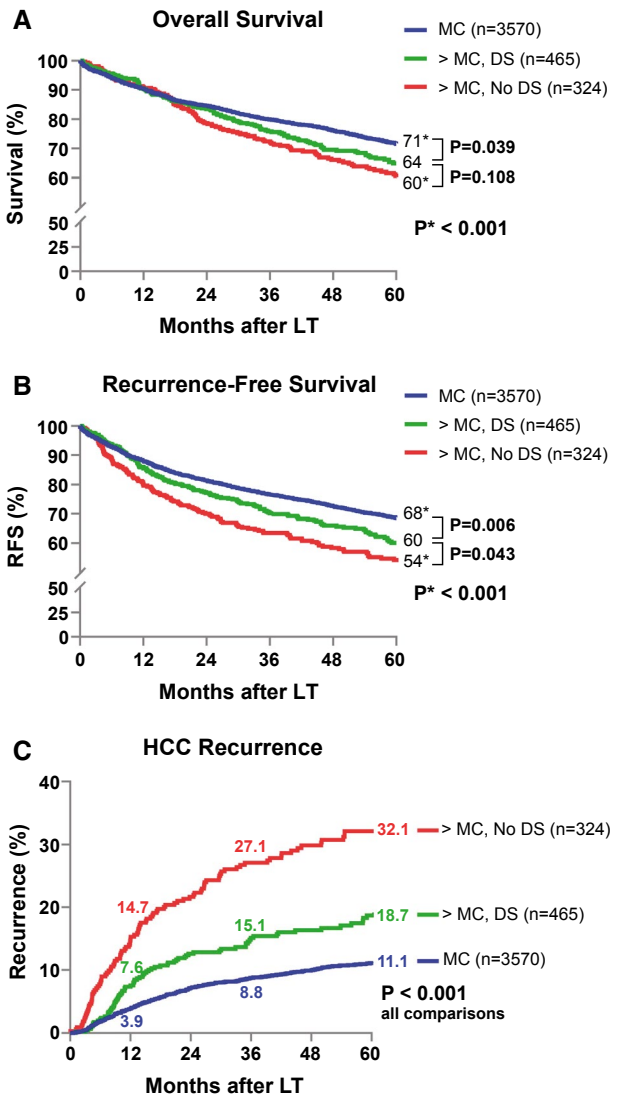

FIG. 1. (A) Kaplan-Meier posttransplant overall survival in patients with HCC who were within Milan Criteria, who were successfully down-staged, and who were not down-staged. (B) Kaplan-Meier posttransplant recurrence-free survival in patients with HCC who were within Milan Criteria, who were successfully down-staged, and who were not down-staged. (C) Kaplan-Meier posttransplant HCC recurrence in patients with HCC who were within Milan Criteria, who were successfully down-staged, and who were not down-staged. Abbreviations: DS, down-staged; LT, liver transplant; MC, Milan Criteria; No DS, non–down-staged; RFS, recurrence-free survival.

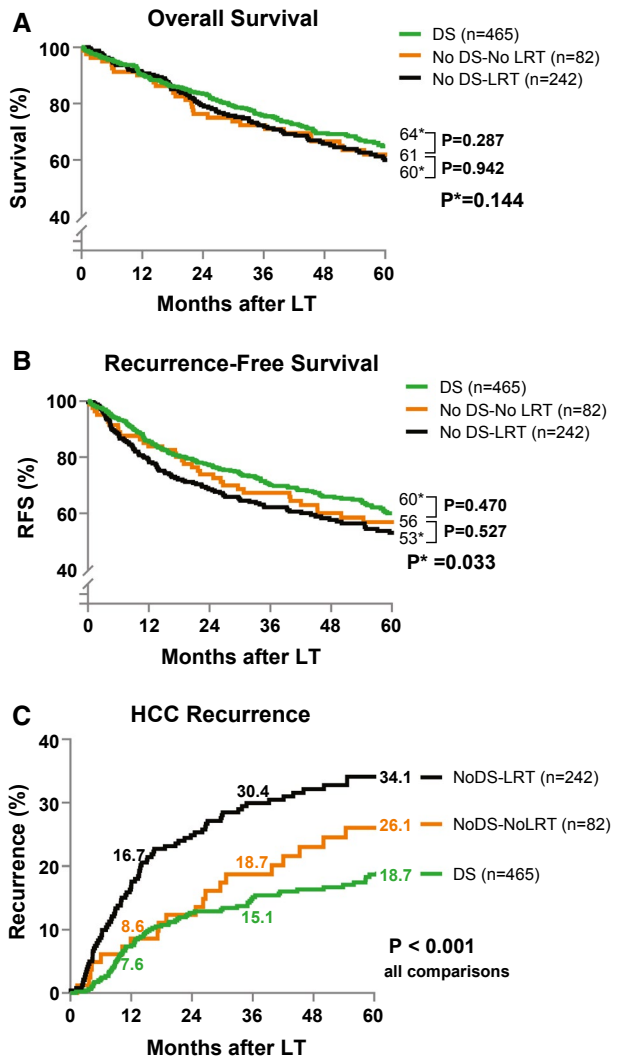

FIG. 2. (A) Kaplan-Meier posttransplant overall survival in patients with HCC who received LRT and were successfully down-staged, received LRT and were not down-staged, and did not receive LRT. (B) Kaplan-Meier posttransplant recurrence-free survival in patients with HCC who received LRT and were successfully down-staged, received LRT and were not down-staged, and did not receive LRT. (C) Kaplan-Meier posttransplant HCC recurrence in patients with HCC who received LRT and were successfully down-staged, received LRT and were not down-staged, and did not receive LRT. Abbreviations: DS, down-staged; LT, liver transplant; NoDS-LRT, non–down-staged, received locoregional therapy; NoDS-No LRT, non-downstaged, did not receive locoregional therapy; RFS, recurrence-free survival.

recipients (>12 months HR = 0.38, CI 0.10-1.44, P = 0.154). To evaluate whether this effect differed in patients who were successfully down-staged prior to LT, we performed a sensitivity analysis evaluating predictors of tumor recurrence in only down-staged patients (Supporting Table S3). We similarly found no association of wait time with recurrence after controlling for AFP response, etiology of cirrhosis, and explant characteristics including vascular invasion, tumor differentiation, and pathologic maximum diameter.

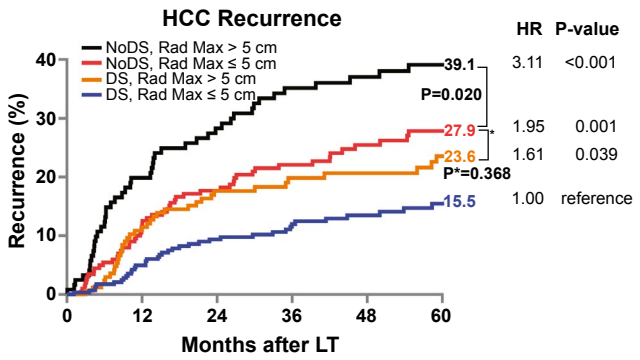

FIG. 3. Kaplan-Meier posttransplant HCC recurrence in HCC patients who were successfully downstaged and had a maximum radiologic tumor diameter >5 cm, successfully downstaged and had a maximum radiologic tumor diameter <5 cm, not downstaged and had a maximum radiologic tumor diameter >5 cm, and not not downstaged and had a maximum radiologic tumor diameter <5 cm. Abbreviations: DS, downstaged; HCC, hepatocellular carcinoma; LRT, locoregional therapy; LT, liver transplant; NoDS, non–down-staged; rad max, radiological maximum tumor diameter; RFS, recurrence free survival.

In the non–down-staged subset, even after simultaneously controlling for pre- and post-LT characteristics, receiving LRT and not being successfully down-staged was an independent predictor of post-LT HCC recurrence (HR = 2.33, CI 1.43-3.85; $P < 0.001$) compared with non-DS patients not receiving LRT (HR = 1.00, reference), with a model C-statistic of 0.784.

We subsequently performed an IPTW survival analysis[16] to account for the probability of receiving LRT and evaluate the true effect of LRT on post-LT HCC recurrence. Comparison of potential confounders between HCC recipients with and without LRT in both the unweighted and weighted sample confirmed that the propensity matching successfully balanced the two groups across demographics, laboratory parameters, treatment characteristics, and explant pathology, as indicated by nonsignificant differences in the weighted samples across all covariates (Supporting Table S4). Using this propensity-matched weighted sample, our IPTW competing risk Cox regression model found that the adjusted hazard ratio for the effect of LRT on post-LT HCC recurrence remained statistically significant (HR = 1.82; CI 1.12-2.94; $P = 0.014$).

TABLE 3. Multivariate Predictors of HCC Recurrence in Non–Down-Staged Patients

	Multivariable Analysis		
Variable	HR	95% CI	*P* Value
Treatment status			
Non–down-staged, not treated	1.00	Reference	Reference
Non–down-staged, treated	2.33	1.43-3.85	<0.001
Patient factors			
Hepatitis C virus	0.55	0.31-0.95	0.033
Neutrophil-to-lymphocyte ratio (per log unit increase)	2.06	1.29-3.30	0.003
Pre-LT AFP (per 50% increase)	1.07	1.02-1.12	0.008
Explant pathology			
Vascular invasion			
None	1.00	Reference	Reference
Microvascular invasion	2.31	1.45-3.67	<0.001
Macrovascular invasion	2.54	1.36-4.76	0.004
Pathologic maximum tumor diameter (per 50% increase)	1.21	0.99-1.48	0.065
Pathologic differentiation			
Well	1.00	Reference	Reference
Moderate	4.64	1.88-11.46	<0.001
Poor	5.42	1.91-15.42	0.002
LT wait-list time			
>12 months	0.38	0.10-1.44	0.154
<12 months	1.00	Reference	Reference

Abbreviations: AFP, alpha-fetoprotein; LT, liver transplant; Model C-statistic, 0.784.

Discussion

For the past 2 decades, the Milan Criteria has been the gold standard criteria for the selection of patients with unresectable HCC for liver transplantation. However, with the longstanding success of LT as a curative treatment for HCC, the transplant community has recently expanded LT eligibility criteria to maximize survival benefit.[9] In this context, tumor down-staging has become an accepted selection tool to identify patients with HCC initially beyond MC who will nonetheless maintain preserved cancer outcomes following LT. Although liberalizing selection criteria is a welcomed advance, gaining a better understanding of the outcomes in patients beyond Milan Criteria, the impact of down-staging, and factors that predict a successful posttransplant course is critical. Retrospective and prospective studies reporting acceptable rates of post-LT HCC recurrence in

beyond-MC patients who are down-staged have been limited to small single-center experiences or a single UNOS region.[10,13] Whether these reported success rates and post-LT outcomes are generalizable on a national scale is largely unknown. Furthermore, these studies have lacked detailed tumor characteristics to identify factors associated with successful down-staging. Using granular data available from the U.S. Multicenter HCC Transplant Consortium, we herein report the largest analysis to date of LT recipients with HCC tumors beyond MC at presentation and assess the impact of down-staging on HCC recurrence and post-LT survival.

We observed acceptable 5-year post-LT overall survival of 63% and recurrence-free survival of 57% in the 789 patients with HCC presenting with tumors beyond MC, with an overall 5-year HCC recurrence incidence of 24%. In line with single-center reports,[5,17] successfully down-staged patients had superior 5-year RFS (60% vs. 54%; $P = 0.043$) and significantly lower 5-year HCC recurrence incidence (19% vs. 32%) compared with non–down-staged LT recipients, validating the current practice of prioritizing patients who demonstrate excellent response to LRT. However, patients who were successfully down-staged still had higher 5-year recurrence rates (18.7% vs. 11.1%, $P < 0.001$) and lower 5-year overall survival (64.3% vs. 71.3%, $P = 0.039$) compared with patients within MC. This finding differs from prior literature, which highlights similar recurrence and survival in down-staged patients compared with LT-recipients presenting within MC.[10,11,13,18] A single-center study by Yao et al.[10] observed a 5-year post-LT survival of 77.8% and recurrence-free probability of 90.8% in 64 DS patients, compared with 81% and 88% in 332 MC patients; however, only 3.2% of DS patients had vascular invasion, and none had poorly differentiated tumors. Another multicenter study of patients at three transplant centers within UNOS region 5 estimated a 5-year post-LT overall survival rate of 79.7% and recurrence-free probability of 87.3% in 109 patients who were successfully down-staged; this study similarly reported low rates of vascular invasion or poorly differentiated tumors.[13] By contrast, in our study, a greater proportion of successfully DS patients had unfavorable tumor characteristics, including 26.3% vascular invasion and 11.2% poor differentiation, which may have translated to worse post-LT outcomes. Furthermore, those prior studies were conducted at centers in UNOS region 5, which has one of the longest wait times in the country, and may have favored transplanting patients who were able to maintain a longer period of stability without dropout on the wait list. Our findings may also be due to the greater heterogeneity of patients in our consortium, which comprises 20 different transplant centers across 10 UNOS regions, where varying center-specific practice patterns, experience, waiting times and access to organs, and diversity in the LT recipient population may reflect the "real world" outcomes that can be expected with liberalization of tumor size criteria.

One objective of this multicenter study was to evaluate factors associated with down-staging success. Among pretransplant factors, serum AFP response to LRT was a significant predictor of down-staging success. Patients who had abnormal initial pre-LRT AFP that normalized to <20 after LRT had a 1.82 times greater odds of successful down-staging compared with patients who had an abnormal AFP that did not improve with LRT. It is becoming increasingly clear that AFP response to LRT may represent an important dynamic marker of aggressive tumor biology. In our cohort, partial AFP response without normalization of AFP did not predict down-staging success, and the association of AFP response with down-staging success was only significant if AFP completely normalized. Perhaps this is not entirely surprising as non-normalized AFP potentially indicates viable tumor on imaging. However, this is certainly not to say that a decrease in AFP in general doesn't positively impact post-LT outcomes such as HCC recurrence. The positive impact of a decreasing AFP prior to LT was observed in the 3,601 recipients within MC undergoing bridging LRT from the U.S. Multicenter HCC Transplant Consortium patients, where a greater improvement in pre-LT AFP was associated with a lower risk of post-LT HCC recurrence.[4] Similarly, in a multicenter U.S. study that included 16% of patients presenting with tumors beyond Milan criteria, post-LT HCC recurrence was impacted by the maximum pre-LT AFP and the degree of reduction.[19] Our findings contribute to the mounting evidence arguing for the inclusion of dynamic AFP changes in HCC LT prioritization in patients beyond MC.

We also found no major differences in the type of LRT received among those who were down-staged and not down-staged (Supporting Table S1). Accordingly, LRT modality did not predict the likelihood of being

down-staged in either univariate or multivariate analysis (Table 2), similar to prior studies.[4,12,13,20] In the present study, the number of LRTs also did not impact down-staging success. Although an increasing number of treatments trended towards significance in univariate analysis, LRT number did not independently predict successful down-staging in multivariate analysis, suggesting that other tumor-related factors may play a bigger role in predicting success of down-staging.

Another interesting finding was that longer wait times were associated with greater down-staging success. In prior analyses of the UNOS database, short wait time has been associated with increased post-LT recurrence and worse post-LT outcomes,[21,22] presumably because of inability to accurately assess tumor behavior and identify occult metastases when expediting patients to transplant. We also reported an association of wait times with pre-LT down-staging success. In our cohort, we found that a longer wait time of >12 months predicted a greater odds of successful down-staging compared with <6 months. This finding may be prone to selection bias, as patients who were able to maintain a longer period of stability on the wait list without dropout may have had less aggressive tumors. Nevertheless, given that LRT number was not independently predictive of down-staging, our findings do suggest that a longer waiting period may be important for selecting better candidates beyond MC for LT who are able to be down-staged successfully.

Explant pathologic factors were also significant in predicting successful down-staging. Although non–down-staged patients were significantly more likely to have poorly differentiated tumors and micro- and macrovascular invasion, these factors surprisingly did not predict successful down-staging in multivariate analysis after controlling for AFP response to LRT, which, similar to these pathologic characteristics, is a surrogate for underlying tumor biology. However, explant pathologic tumor number and maximum tumor diameter were independent predictors of down-staging success. LT recipients with more than one tumor or a greater maximum tumor diameter had significantly lower odds of being down-staged, in line with prior single-center studies demonstrating that the probability of DS decreases as tumor burden increases.[23-25]

Consistent with prior studies, tumor size impacted risk of HCC recurrence, even in patients who were able to be successfully down-staged. In both DS and NoDS subgroups, radiologic tumor diameter >5 cm portended a greater risk of post-LT HCC recurrence compared with those with tumor diameter ≤5 cm, with the lowest recurrence rates observed in DS LT recipients with radiologic tumors ≤5 cm. Our findings highlight that not all subgroups of patients meeting UNOS down-staging eligibility criteria are the same and emphasize that there are other important factors in addition to the simple binary characterization of down-staged/not down-staged that predict risk of HCC recurrence. These data support the development of pretransplant models that incorporate not only LRT response but also tumor size and/or burden, AFP response, and other criteria into the assessment of pre-LT candidates. Such models have been previously proposed, such as the TRAIN model,[26] but larger-scale validation studies are needed to apply these models into clinical practice.

Interestingly, longer wait time was not associated with post-LT HCC recurrence in non–down-staged patients who presented with tumors beyond MC. Although prior data have identified wait times as an important predictor of post-LT outcomes, these studies included only patients who were either within MC at presentation or down-staged to within MC prior to transplant.[21,22] In a sensitivity analysis of only down-staged patients evaluating the association of wait time with HCC recurrence, we similarly found no association of wait time with recurrence after controlling for AFP response to LRT and other pre-LT and explant characteristics (Supporting Table S3). Given that both waiting time and AFP response to LRT are dynamic markers of tumor biology, one explanation is that the impact of wait times on post-LT HCC recurrence was muted when simultaneously controlling for patients' dynamic AFP response over the waiting period. Prior analyses from the UNOS databases did not have the benefit of incorporating AFP response. We therefore hypothesize that post-LT HCC recurrence in beyond-MC patients, whether they were down-staged or not, is predominantly driven by their dynamic AFP response to LRT, which, similar to waiting time, is a surrogate for underlying tumor biology. This finding also suggests that wait time may be a less important factor once a patient is able to be successfully down-staged, unlike in patients who present within MC, where wait time appears to be a significant predictor of post-LT outcomes.[21,22]

Another very intriguing finding in our study was that patients who received LRT and were not successfully down-staged surprisingly had worse outcomes compared with non–down-staged patients not receiving any LRT at all, despite having significantly fewer advanced-stage tumors and less macrovascular invasion (Supporting Table S1). To ensure that this observation was not a result of varying patient and tumor characteristics between groups, we performed a multivariate analysis controlling for important pre- and post-LT characteristics. Despite controlling for these factors, non–down-staged patients with HCC receiving LRT had an independently increased rate of HCC recurrence compared with non–down-staged patients not receiving LRT (HR = 2.33, $P < 0.001$; Table 3). Even after propensity matching between groups to account for selection bias, receiving LRT and not being down-staged conferred an increased hazard rate (HR = 1.82) for developing post-LT recurrence compared with nontreated, non–down-staged patients. One potential explanation for this phenomenon is that the inability to be down-staged by LRT may serve as a surrogate for a more unfavorable tumor biology that is otherwise not captured by the standard well-characterized laboratory markers and tumor-related explant characteristics. Conversely, in this subset of treated non–down-staged patients, LRT itself may be unveiling a more aggressive tumor behavior than if the lesion were left untreated.

That LRT itself may negatively impact HCC outcomes has been hypothesized before.[4,27-29] A retrospective analysis of 384 patients with HCC who underwent LT showed significantly higher HCC recurrence rates in patients with partial necrosis as compared with those with complete or no tumor necrosis (22.6% vs. 5.2% and 6.1%, respectively; $P < 0.001$), which was hypothesized to be due to more lymphatic metastases and greater levels of circulating angiogenic factors in the LRT-treated subgroup.[28] In a much larger analysis of 3,601 LT recipients within MC, treatment with LRT and failure to get complete pathologic response resulted in a significantly greater risk of HCC recurrence (HR = 1.32, $P = 0.044$), even after controlling for important pretransplant and tumor-related characteristics.[4] Other studies in patients undergoing liver tumor resection have shown that the tumor microenvironment generated after tumor removal can impact recurrence. In one study of patients with metastatic colorectal cancer to the liver, hepatic ischemic stress after liver resection induced the formation of neutrophil extracellular traps (NETs), materials within neutrophils that were expelled into the local environment. These NETs were found to promote migration of tumor cells into the surrounding blood vessels and were associated with early metastatic recurrence.[30] In another study of mice with nonalcoholic steatohepatitis (NASH), inhibition of NETs led to a reduction in the progression of NASH to HCC.[31] These findings collectively suggest that ischemia in the hepatic tumor microenvironment could play a role in cancer progression. This study showed that LRT itself may independently predict inferior outcomes in the subset of patients who are not down-staged after accounting for multiple prognostic factors. Regardless of whether this is due to the paradoxical unmasking of more virulent tumor biology by LRT not otherwise captured by standard tumor-related variables or pro-oncogenic changes to the tumor microenvironment by LRT, our findings warrant further investigation into the potential role of LRT in modifying the natural history of HCC.

A strength of our database is the inclusion of LT recipients from 20 different transplant centers encompassing 10 UNOS regions. Although our post-LT recurrence rates are higher than what has been reported in single-center studies, we believe our results reflect real-world practice and are thus more generalizable to all patients with HCC across the United States. Furthermore, we were able to incorporate individual wait times into our analyses to account for the potential contribution of differing wait times between regions. The large size of our cohort allowed us to identify predictors of successful down-staging and HCC recurrence. Finally, the availability of detailed explant pathologic data allowed for better characterization of the association between tumor-related characteristics and post-LT outcomes.

One of the major limitations is that our study's data set does not include information about patients at each center who were delisted as a result of tumor progression, precluding an intent-to-treat analysis. Therefore, we could not identify the factors associated with wait-list dropout. We also could not account for any variations in practice patterns, such as down-staging strategies, between different transplant centers; however, this also reflects the generalizability of our data to the real world.

In the largest national multicenter experience of patients with HCC with tumors beyond MC undergoing LT, we report excellent rates of post-LT survival and HCC recurrence in patients presenting beyond MC, with superior RFS and tumor recurrence outcomes in LT recipients who are down-staged. Our findings support the transplant community's expansion to prioritize access to LT for patients with HCC who have been successfully down-staged to within MC. We also found that wait time >12 months, tumor burden, and pre-LT AFP normalization to LRT but not LRT modality or number were key predictors of successful down-staging, emphasizing the importance of using dynamic evaluations of tumor response to guide LT selection and provide reliable predictions of prognosis in patients beyond MC. Finally, we identified LRT as an independent predictor of HCC recurrence in non–down-staged patients, suggesting that LRT itself may have a paradoxically aggravating role in a subset of patients who do not respond to treatment or, at the very least, that the lack of response to LRT is a surrogate for a more aggressive tumor biology that is not captured by other well-characterized tumor-related factors. Ultimately, a better understanding of the impact of LRT and the biologic underpinnings of HCC tumor behavior will allow us to identify patients who will gain the most benefit from transplant while also preserving excellent outcomes in the landscape of a growing organ shortage.

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Supporting Information

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