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National Experience on Down-Staging of Hepatocellular Carcinoma Before Liver Transplant: Influence of Tumor Burden, Alpha-Fetoprotein, and Wait Time

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BACKGROUND AND AIMS: United Network for Organ Sharing (UNOS) recently implemented a national policy granting priority listing for liver transplantation (LT) in patients who achieved down-staging of hepatocellular carcinoma (HCC) to Milan criteria. We aimed to evaluate the national experience on down-staging by comparing two down-staging groups with (1) tumor burden meeting UNOS down-staging (UNOS-DS) inclusion criteria and (2) "all-comers" (AC-DS) with initial tumor burden beyond UNOS-DS criteria versus patients always within Milan.

APPROACH AND RESULTS: This is a retrospective analysis of the UNOS database of 3,819 patients who underwent LT from 2012 to 2015, classified as always within Milan (n = 3,276), UNOS-DS (n = 422), and AC-DS (n = 121). Median time to LT was 12.8 months in long wait regions, 6.5 months in mid wait regions (MWR), and 2.6 months in short wait regions (SWR). On explant, vascular invasion was found in 23.7% of AC-DS versus 16.9% of UNOS-DS and 14.4% of Milan (P = 0.002). Kaplan-Meier 3-year post-LT survival was 83.2% for Milan, 79.1% for UNOS-DS (P = 0.17 vs. Milan), and 71.4% for AC-DS (P = 0.04 vs. Milan). Within down-staging groups, risk of post-LT death in multivariable analysis was increased in SWR or MWR (hazard ratio [HR], 3.1; P = 0.005) and with alpha-fetoprotein (AFP) ≥ 100 ng/mL at LT (HR, 2.4; P = 0.009). The 3-year HCC recurrence probability was 6.9% for Milan, 12.8% for UNOS-DS, and 16.7% for AC-DS (P < 0.001). In down-staging groups, AFP ≥ 100 (HR, 2.6; P = 0.02) was the only independent predictor of HCC recurrence.

CONCLUSIONS: Our results validated UNOS-DS criteria based on comparable 3-year survival between UNOS-DS and Milan groups. Additional refinements based on AFP and wait time may further improve post-LT outcomes in down-staging groups, especially given that reported 3-year recurrence was higher than in those always within Milan criteria. (Hepatology 2019;0:1-12).

The Milan criteria[1] have stood the test of time and remained the benchmark for the selection of candidates with hepatocellular carcinoma (HCC) for liver transplantation (LT) for more than 2 decades. As the incidence of HCC continues to rise,[2] HCC has become a leading indication for LT in the United States.[3,4] Expanding the LT indications for HCC to meet this growing demand but also ensuring acceptable post-LT outcomes has been a challenging task.[5-7] Over time, the focus has shifted to incorporate markers of tumor biology into LT selection guidelines that have traditionally been based only on tumor size and number.[8] In this context, many studies have demonstrated that combining alpha-fetoprotein (AFP) with tumor burden discriminates prognosis after LT better than using tumor

Abbreviations: AC-DS, all-comers down-staging; AFP, alpha-fetoprotein; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; LRT, local regional therapy; LT, liver transplantation; LWR, long wait region; MELD, Model for End-Stage Liver Disease; MWR, mid wait region; OR, odds ratio; RETREAT, Risk Estimation of Tumor Recurrence After Transplant; SWR, short wait region; UCSF, University of California, San Francisco; UNOS, United Network for Organ Sharing; UNOS-DS, UNOS down-staging.

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burden alone.[9-11] Another important prognostic marker is response to local regional therapy (LRT) prior to LT.[12-16] Evidence has continued to emerge suggesting that patients who exhibit tumor progression despite LRT have significantly worse post-LT outcomes when compared with those who demonstrate treatment response or stable disease following LRT.[13-16]

Rather than simply pushing the upper limits in tumor burden, down-staging combines expanded criteria with response to LRT, and has now moved to the frontline in selecting suitable LT candidates with initial tumors exceeding Milan criteria. The rationale behind tumor down-staging is to select a subgroup of patients with favorable biology and prognosis for LT judged by their objective and sustained response to LRT.[17] Most of the early single-center studies on down-staging were limited by their small sample size and short duration of post-LT follow-up, as well as the lack of well-defined eligibility criteria for down-staging.[17,18] The University of California, San Francisco (UCSF) proposed inclusion criteria for down-staging, first reported in 2005, were based on one lesion >5 cm and ≤8 cm, two or three lesions each ≤5 cm, or four to five lesions each ≤3 cm with a total tumor diameter ≤8 cm. In the latest published series from UCSF,[19] the 5-year post-LT survival after successful tumor down-staging to within Milan criteria was 78%, essentially identical to that of a control group with HCC always within Milan criteria before LT, and only 8% of the down-staging group experienced post-LT HCC recurrence. In the first multicenter study on down-staging using the UCSF protocol in United Network for Organ Sharing (UNOS) Region 5, an excellent 5-year post-LT survival of 80% was demonstrated without obvious center effects.[20] Largely based on these results, a new UNOS policy in early 2017 has adopted the UCSF/Region 5 inclusion criteria for down-staging (UNOS-DS).[19] Patients with initial tumor burden meeting UNOS-DS inclusion criteria who achieve successful down-staging to within Milan criteria are eligible to receive automatic approval for Model for End-Stage Liver Disease (MELD) exception for LT.[21]

Because Region 5 has one of the longest wait times to LT in the United States, and very short wait time has been linked with worse post-LT outcomes in HCC,[4,22-24] the results from Region 5 may not be generalizable across other regions. Additionally, little is known about the post-LT outcomes after down-staging in patients with initial tumor burden exceeding UNOS-DS criteria. Prior to UNOS adopting the UCSF/Region 5 down-staging protocol as a national policy in 2017, many centers across different regions have already applied tumor down-staging without standardized inclusion criteria.[21]

In the present study, we analyzed the UNOS database and aimed to evaluate the national experience on down-staging, and we compared post-LT outcomes between those with HCC always within Milan criteria versus two different down-staging groups classified by initial tumor burden meeting UNOS-DS criteria and "all-comers" down-staging (AC-DS) group with initial tumor burden beyond UNOS-DS criteria. We also sought to evaluate pre-LT factors predicting post-LT survival and HCC recurrence in the down-staging groups as well as the impact of regional differences in wait time on post-LT outcomes after tumor down-staging.

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Patients and Methods

STUDY DESIGN AND PATIENT POPULATION

This study included consecutive patients in the UNOS database (Standard Transplant Analysis and Research files released in December 2016) aged 18 years and older who received MELD exception for HCC and underwent LT between April 2012 and September 2015. The study start date was chosen to coincide with the time when UNOS/Organ Procurement and Transplantation Network initiated the explant pathology form. Patients were classified into three categories based on their maximum radiographic tumor burden (including tumor number and size) as reported on their MELD exception applications. The "Milan" group included only patients with HCC always within Milan criteria (one lesion ≤5 cm or two to three lesions ≤3 cm) at each exception application. The "UNOS-DS" group met the UNOS down-staging inclusion criteria (one lesion >5 and ≤8 cm, two to three lesions with at least one >3 cm and ≤5 cm with total tumor diameter ≤8 cm, or four to five lesions each ≤3 cm with total tumor diameter ≤8 cm)[19] on at least one exception application but never exceeded the criteria. Patients in the "AC-DS" group had initial tumor burden exceeding UNOS-DS inclusion criteria on at least one exception application. There was no upper limit of tumor number or diameter for the AC-DS cohort. Both the UNOS-DS and AC-DS groups were required to receive MELD exception for HCC that had been down-staged to within Milan criteria on their last exception application prior to LT. Patients without evidence of HCC on explant who had not received LRT prior to LT (HCC misdiagnosis) as well as patients with either intrahepatic cholangiocarcinoma or mixed HCC/cholangiocarcinoma on explant were excluded.

Study variables collected from the UNOS database at the time of listing with MELD exception included age, sex, race/ethnicity, etiology of liver disease, and listing UNOS region. The size and number of HCC lesions at inclusion was determined at time of initial priority exception for the Milan cohort and when first beyond Milan criteria for the UNOS-DS and when first beyond UNOS-DS criteria for the AC-DS cohorts. The percentage of patients who underwent LRT while on the wait list and the time from first MELD exception to LT was also collected, as was MELD score at LT. The 11 UNOS regions were subdivided based on median time from initial listing with MELD exception to LT with >9, 3-9, and <3 month wait-list times representing long (regions 1, 5, 9 [LWR]), mid (2, 4, 6, 7, 8 [MWR]), and short wait regions (3, 10, 11 [SWR]), respectively. Per UNOS listing policy, patients underwent contrast-enhanced computed tomography or magnetic resonance imaging at a minimum of once every 3 months after LT listing.

LIVER TRANSPLANT–RELATED VARIABLES

The AFP closest to the date of LT (within 90 days prior to LT) was obtained from the liver exception data. Presence of vascular invasion and number and size of viable lesions were obtained from the explant data and used to determine both tumor stage and the individual Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score.[25] The three components of the RETREAT score are AFP at LT, microvascular invasion, and the sum of the largest viable tumor plus number of viable tumors on explant. The methods used to create the RETREAT score have been described.[22] Explant pathology was also reviewed to determine histologic grade based on the modified Edmondson criteria.[26]

HCC RECURRENCE

To identify patients with post-LT HCC recurrence, liver malignancy follow-up data and cause of death variables underwent physician review (author N.M.). Records indicating posttransplant recurrence of pretransplant malignancy or a cause of death indicating HCC or metastatic malignancy were classified as having HCC recurrence.

OUTCOMES AND STATISTICAL ANALYSIS

The primary outcome was post-LT survival, and the secondary outcome was post-LT HCC recurrence. Outcomes were assessed for the overall cohort and stratified by wait time region. Clinical and tumor characteristics were summarized using

medians and interquartile ranges (IQRs) for continuous variables and proportions for categorical variables. Characteristics including RETREAT score were stratified by tumor burden category (Milan, UNOS-DS, and AC-DS) and compared with Kruskal-Wallis and Pearson's chi-squared tests, as appropriate.

Observed HCC recurrence and post-LT survival probabilities and 95% confidence intervals (CIs) were estimated at 1 and 3 years using the Kaplan-Meier method and compared by tumor burden category and wait time region using the log-rank test. For post-LT survival, patient follow-up was measured from the date of LT to death (event) with patients remaining alive censored at the date of retransplant or last follow-up. For post-LT HCC recurrence, patient follow-up was measured from the date of LT to HCC recurrence or HCC-related death (event) with patients censored at the date of non-HCC death or last follow-up. For patients in the down-staging groups (UNOS-DS and AC-DS), the association of explanatory variables known prior to transplant (i.e., exclusion of explant data) was explored using univariate and multivariable hazard ratios (HRs) and 95% CIs estimated by Cox proportional hazards regression for post-LT survival and HCC recurrence. Explanatory variables with a univariate P value < 0.1 were included in the multivariable analysis with the final model selected by backward elimination (P for removal >0.05).

The ability of the RETREAT score to discriminate between events and nonevents, for the outcome of HCC recurrence, was assessed using the overall C-index[27] with bootstrap 95% CIs. For HCC recurrence, net reclassification index[28] evaluated improvement in model performance by quantifying the proportion of correct risk reclassification when using RETREAT score versus explant-based Milan criteria to predict risk. Net reclassification improvement was evaluated up to 3 years after LT using *a priori* recurrence risk categories (<5%, 5% to <10%, 10% to <20%, and ≥20%). Correct risk reclassification occurred when RETREAT score predicted probabilities reclassified patients with recurrence into higher risk categories and patients without recurrence into lower risk categories compared with estimates by explant Milan criteria. Statistical analyses were performed using SAS version 9.4 (Cary, NC) and Stata/IC 14.2 (College Station, TX).

The study was approved by the UCSF Institutional Review Board. The study received expedited approval with minimal study risk assignment and without informed consent required.

Results

BASELINE AND WAIT-LIST CHARACTERISTICS

Of the 3,900 patients identified with HCC who received priority listing with MELD exception and underwent LT, 81 were excluded as a result of explant demonstrating cholangiocarcinoma (n = 16), unknown tumor burden (n = 29), or no HCC despite lack of LRT before LT (n = 36). The remaining 3,819 patients constituted the final cohort, of whom 3,276 (85.8%) were always within Milan criteria, 422 (11.0%) met UNOS-DS criteria, and 121 (3.2%) exceeded these criteria and were classified as AC-DS.

The baseline and wait-list characteristics of the study cohort stratified by initial tumor burden criteria are summarized in Table 1. The median age at listing with MELD exception was 60 years (IQR, 56-63), and 77.4% were men. The most common race/ethnicities were white (68.8%), Hispanic (13.4%), black (9.4%), and Asian (7.1%). Hepatitis C was the most common etiology of liver disease (62.6%), followed by nonalcoholic fatty liver disease (7.8%), alcoholic liver disease (7.3%), and hepatitis B (5.7%). Overall, 21.8% were listed in LWR, 42.4% in MWR, and 35.8% in SWR. In the AC-DS cohort, 44.6% were listed in SWR, with only 12.4% from LWR (P = 0.04).

Median total tumor diameter at listing with MELD exception was 2.8 cm (IQR, 2.3-3.7) in the Milan group compared with 5.8 cm (5.3-6.5) at the time for inclusion in the UNOS-DS cohort and 9.3 cm (8.5-10.6) at inclusion in the AC-DS cohort (P < 0.001). Median number of lesions was 1 (IQR, 1-1) in the Milan cohort compared with 2 (1-2) in the UNOS-DS and 2 (2-4) in the AC-DS cohort (P < 0.001). Initial median AFP level overall was 10 ng/mL (IQR, 5-32) and was highest in the Milan cohort (P < 0.001). While on the wait list, 92.1% received at least one LRT, with the highest proportion in the UNOS-DS cohort (98.6%) and the AC-DS cohort (96.7%; P < 0.001 vs. 91.1% in the Milan cohort). On the last reported cross-sectional imaging prior to LT, median total tumor diameter in the Milan group was 2.0 cm compared with 2.6 cm

TABLE 1. Baseline and Wait-List Clinical Characteristics of the Study Cohort Stratified by Initial Tumor Burden

Characteristics	Overall (n = 3,819)	Milan (n = 3,276)	UNOS-DS (n = 422)	AC-DS (n = 121)	*P* Value
Median age (IQR), years	60 (56-63)	60 (56-63)	60 (57-64)	60 (56-65)	0.007
Male (%)	2,957 (77.4)	2,512 (76.7)	343 (81.3)	102 (84.3)	0.02
Race/ethnicity (%)					0.80
White	2,626 (68.8)	2,259 (69.0)	280 (66.4)	87 (71.9)	
Hispanic	511 (13.4)	438 (13.4)	60 (14.2)	13 (10.7)	
Black	359 (9.4)	305 (9.3)	40 (9.5)	14 (11.6)	
Asian	271 (7.1)	231 (7.1)	34 (8.1)	6 (5.0)	
Etiology of liver disease (%)					0.25
Hepatitis C	2,390 (62.6)	2,056 (62.8)	256 (60.7)	78 (64.5)	
NAFLD	298 (7.8)	261 (8.0)	29 (6.9)	8 (6.6)	
Alcohol	280 (7.3)	239 (7.3)	27 (6.4)	14 (11.6)	
Hepatitis B	219 (5.7)	180 (5.5)	35 (8.3)	4 (3.3)	
Autoimmune*	76 (2.0)	67 (2.1)	7 (1.7)	2 (1.7)	
UNOS wait region (%)					0.04
Long (1, 5, 9)	833 (21.8)	728 (22.2)	90 (21.3)	15 (12.4)	
Mid (2, 4, 6, 7, 8)	1,619 (42.4)	1,374 (41.9)	193 (45.7)	52 (43.0)	
Short (3, 10, 11)	1,367 (35.8)	1,174 (35.8)	139 (32.9)	54 (44.6)	
Initial total tumor diameter (IQR), cm†	3.1 (2.3-4.4)	2.8 (2.3-3.7)	5.8 (5.3-6.5)	9.3 (8.5-10.6)	<0.001
Initial largest lesion size (IQR), cm†	2.6 (2.1-3.4)	2.4 (2.1-3.0)	4.3 (3.5-5.6)	5.5 (4.3-7.6)	<0.001
Initial number of lesions (IQR)†	1 (1-2)	1 (1-1)	2 (1-2)	2 (2-4)	<0.001
Initial AFP (IQR), ng/mL†	10 (5-32)	11 (5-34)	9 (4-26)	7 (4-16)	<0.001
AFP at LT					
Median (IQR), ng/mL	9 (4-25)	9 (4-26)	8 (4-23)	6 (4-13)	0.004
AFP at LT < 20 (%)	2,684 (70.3)	2,278 (69.5)	307 (72.7)	99 (81.8)	
AFP at LT 20-99 (%)	751 (19.7)	650 (19.8)	85 (20.1)	16 (13.2)	0.01
AFP at LT 100-999 (%)	348 (9.1)	318 (9.7)	24 (5.7)	6 (5.0)	
AFP at LT > 1,000 (%)	36 (0.9)	30 (0.9)	6 (1.4)	0 (0)	
Median MELD at LT (IQR)	11 (8-15)	11 (8-15)	11 (8-15)	10 (8-14)	0.005
Last total tumor diameter prior to LT (IQR), cm	2.0 (0.0-3.1)	2.0 (0.0-2.9)	2.6 (0.0-5.0)	4.0 (0.5-7.3)	<0.001
Last largest lesion size prior to LT (IQR), cm	1.7 (0.0-2.5)	1.7 (0.0-2.4)	2.2 (0.0-3.6)	2.8 (0.5-4.5)	<0.001
Last number of lesions prior to LT (IQR)	1 (1-1)	1 (1-1)	1 (1-2)	1 (1-2)	<0.001
Received LRT (%)	3,517 (92.1)	2,984 (91.1)	416 (98.6)	117 (96.7)	<0.001
Time from initial exception to LT (IQR), months	4.9 (2.3-10.1)	4.9 (2.3-9.9)	5.6 (2.6-11.9)	3.8 (2.2-8.0)	0.001

*Includes autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis.
†Determined at time of initial priority exception for the "Milan" cohort, when first beyond Milan criteria for the "UNOS-DS" cohort, and when first beyond UNOS down-staging criteria for the "AC-DS" cohort.

in the UNOS-DS group and 4.0 cm in the AC-DS group ($P < 0.001$).

LIVER TRANSPLANT CHARACTERISTICS

At the time of LT, the median calculated MELD score was 11 (IQR, 8-15) and the median AFP was 9 ng/mL (4-25). Median AFP at LT was lowest in the AC-DS cohort ($P = 0.004$). Overall, the median wait time from listing with MELD exception to LT was 4.9 months (IQR, 2.3-10.1) and was longest in the UNOS-DS cohort at 5.6 months (IQR, 2.6-11.9; $P = 0.001$; Table 1). When stratified by wait region, median time from priority listing to LT was 12.8 months (IQR, 6.8-16.1) in LWR, 6.5 months (3.4-10.1) in MWR, and 2.6 months (1.1-4.2) in SWR ($P < 0.001$).

Explant characteristics of the study cohort stratified by initial tumor burden criteria are summarized in Table 2. In the explant, tumor staging showed no viable tumor as a result of LRT in 29.8%, tumors within Milan criteria in 53.1%, and under-staging to beyond Milan criteria in 17.1%. The probability of under-staging to beyond Milan criteria was

TABLE 2. Explant Characteristics of the Study Cohort Stratified by Initial Tumor Burden

Characteristics	Overall (n = 3,819)	Milan (n = 3,276)	UNOS-DS (n = 422)	AC-DS (n = 121)	*P* Value
Pathologic tumor stage					<0.001
Within Milan	3,167 (82.9)	2,810 (85.8)	285 (67.5)	72 (59.5)	
Beyond Milan	652 (17.1)	466 (14.2)	137 (32.5)	49 (40.5)	
Largest viable lesion (cm) plus number of viable lesions					
Median (IQR)	3.2 (0.0-4.9)	3.1 (0.0-4.5)	4.5 (0.0-6.3)	4.8 (1.8-7.5)	<0.001
0 (%)	1,138 (29.8)	997 (30.4)	112 (26.5)	29 (24.0)	<0.001
1-4.9 (%)	1,728 (45.2)	1,571 (47.9)	125 (29.6)	32 (26.4)	
5-9.9 (%)	906 (23.7)	681 (20.8)	176 (41.7)	49 (40.5)	
>10 (%)	47 (1.2)	27 (0.8)	9 (2.1)	11 (9.1)	
Histologic grade (%)*					0.51
Complete necrosis	677 (18.8)	584 (19.0)	71 (17.4)	22 (18.6)	
Well differentiated	909 (25.2)	792 (25.7)	94 (23.0)	23 (19.5)	
Moderately differentiated	1,746 (48.4)	1,471 (47.8)	211 (51.6)	64 (54.2)	
Poorly differentiated	271 (7.5)	229 (7.4)	233 (8.1)	9 (7.6)	
Vascular invasion (%)†					0.002
None	3,063 (85.0)	2,633 (85.6)	340 (83.1)	90 (76.3)	
Microvascular	476 (13.2)	392 (12.7)	63 (15.4)	21 (17.8)	
Macrovascular	65 (1.8)	52 (1.7)	6 (1.5)	7 (5.9)	
RETREAT score[21]					
Median (IQR)	1 (1-2)	1 (1-2)	2 (1-3)	2 (1-3)	<0.001
0	878 (23.0)	760 (23.2)	292 (21.8)	26 (21.5)	
1	1,220 (31.9)	1,106 (33.8)	90 (21.3)	24 (19.8)	
2	793 (20.8)	644 (19.7)	118 (28.0)	31 (25.6)	<0.001
3	449 (11.7)	380 (11.6)	55 (13.0)	14 (11.6)	
4	292 (7.6)	233 (7.1)	44 (10.4)	15 (12.4)	
>5	187 (4.9)	153 (4.7)	23 (5.4)	11 (9.1)	

*n = 3,603.
†n = 3,604.

significantly higher in the UNOS-DS (32.5%) and AC-DS (40.5%) groups compared with the Milan group (14.2%; $P < 0.001$). The sum of the largest viable lesion (cm) plus number of viable lesions was 3.1 (IQR, 0-4.5) in the Milan cohort, 4.5 (0-6.3) in the UNOS-DS cohort, and 4.8 (1.8-7.5) in the AC-DS cohort ($P < 0.001$). Poorly differentiated tumor grade was found in 7.5% overall, and there were no statistically significant differences in histologic tumor differentiation among the different subgroups (Milan vs. UNOS-DS vs. AC-DS; $P = 0.51$). Micro- and macrovascular invasion were found in 13.2% and 1.8%, respectively, in the entire cohort, with the highest incidence in the AC-DS group (17.8% and 5.9%, respectively; $P = 0.002$). Median RETREAT score was highest in the AC-DS cohort, with 21.5% having a RETREAT score of ≥4 compared with 15.8% in the UNOS-DS group and 12.5% in the Milan group ($P < 0.001$).

POSTTRANSPLANT OUTCOMES STRATIFIED BY TUMOR BURDEN CRITERIA AND WAIT REGION

Median post-LT follow-up was 1.9 years (IQR, 1.0-2.4). The Kaplan-Meier 3-year post-LT survival was 83.2% (95% CI, 81.3-85.0) in the Milan group, 79.1% (95% CI, 73.6-83.5) in the UNOS-DS group ($P = 0.17$ vs. Milan), and 71.4% (95% CI, 58.1-81.2) in the AC-DS group ($P = 0.04$ vs. Milan; Fig. 1A). Among patients in the Milan group, no significant difference in post-LT survival was detected by wait region. However, within UNOS-DS, the 3-year post-LT survival was lower in MWR (72.5%) and SWR (78.7%) compared with LWR (92.3%; $P = 0.009$; Fig. 1B,C). Similar 3-year survival trends were seen in the AC-DS group (LWR, 93.3%; MWR, 65.7%; SWR, 73.0%), although these differences did not reach statistical significance (Fig. 1D).

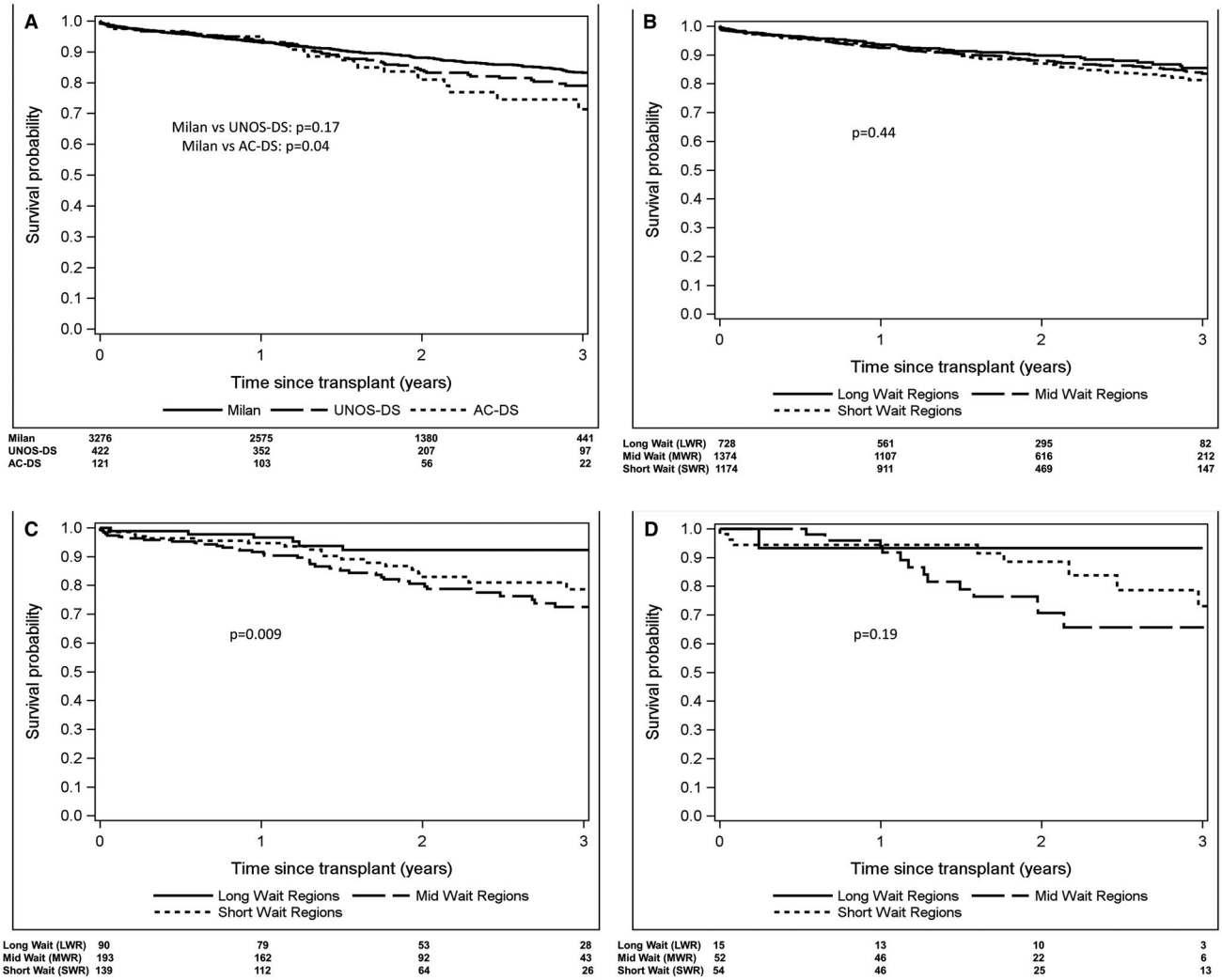

FIG. 1. Kaplan-Meier probability of post-LT survival stratified by initial tumor burden criteria (A) for all regions as well as by wait time region (long vs. mid vs. short) for (B) Milan, (C) UNOS down-staging (UNOS-DS), and (D) All-comers (AC-DS).

Post-LT HCC recurrence was observed in 5.1% of the entire cohort, including 4.4% in Milan, 9.2% in UNOS-DS, and 10.7% in AC-DS ($P < 0.001$). The Kaplan-Meier probability of HCC recurrence at 3 years after LT was 6.9% (95% CI, 5.7-8.2) for Milan, 12.8% (9.2-17.5) for UNOS-DS, and 16.7% (9.1-29.5) for AC-DS ($P < 0.001$; Fig. 2). Post-LT recurrence at 3 years was numerically higher for UNOS-DS in MWR (16.3%) and SWR (12.2%) compared with LWR (7.2%), although this was not statistically significant (P values > 0.2). The median time to HCC recurrence after LT was 11.5 months (IQR, 6.6-18.1) in the entire cohort and did not differ by subgroups based on initial tumor burden ($P = 0.80$).

PREDICTORS OF POST-LT OUTCOMES IN PATIENTS INITIALLY BEYOND MILAN CRITERIA

Using Cox proportional hazards modelling in patients who were ever beyond Milan criteria on imaging (n = 543), we analyzed factors known prior to LT (explant variables excluded) associated with post-LT death and HCC recurrence. In univariate analysis, significant predictors of worse post-LT survival included receiving LT in MWR or SWR and AFP ≥ 100 ng/mL at LT with a trend toward increasing HR for AFP at LT 20-99 (compared with <20 ng/mL). The risk

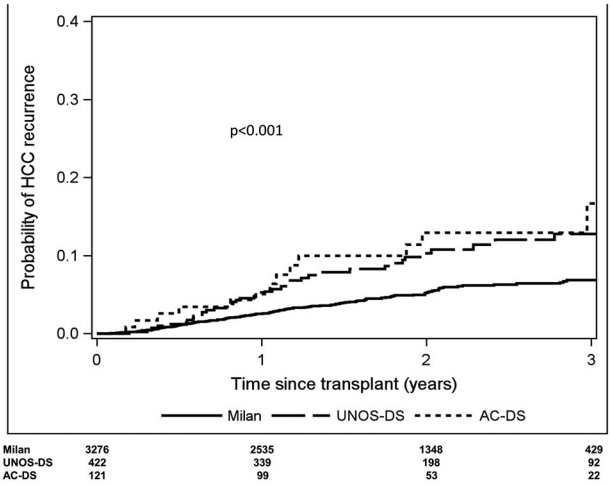

FIG. 2. Kaplan-Meier probability of post-LT HCC recurrence stratified by initial tumor burden criteria.

of death increased with increasing sum of the largest tumor plus the total number of tumors on imaging but did not achieve statistical significance (Table 3). Age, MELD score at LT, initial tumor burden (Milan vs. UNOS-DS vs. AC-DS), and number of tumors and tumor size at study inclusion were not predictive of post-LT survival on univariate analysis. In multivariable analysis, receiving LT in SWR or MWR (HR, 3.07; P = 0.005) and AFP ≥ 100 ng/mL at LT (HR, 2.36; P = 0.009) remained statistically significant predictors of worse post-LT survival (Table 3). In patients ever beyond Milan on pre-LT imaging, the Kaplan-Meier 3-year post-LT probability of survival was 59.5% for patients with an AFP ≥ 100 ng/mL compared with 80.6% for patients with an AFP < 20 and 72.1% for patients with an AFP 20-99 ng/mL (P = 0.01; Fig. 3). Using logistic regression, factors predicting explant tumor stage beyond Milan included AFP ≥ 20 at LT (odds ratio [OR], 2.40; 95% CI, 1.62-3.58; P < 0.001), total tumor diameter (OR, 1.10; 95% CI, 1.03-1.17; P = 0.006), and the number of lesions plus the size of the largest lesion (cm) ≥5 on the last imaging prior to LT (OR, 1.74; 95% CI, 1.20-2.52; P = 0.004).

When analyzing factors known prior to LT in patients within the two down-staging groups (n = 543), the only independent predictor of post-LT HCC recurrence was AFP ≥ 100 ng/mL at LT (HR, 2.59; 95% CI, 1.15-5.86; P = 0.02 compared with AFP < 100). Age, MELD score at LT, initial tumor burden (UNO-DS vs. AC-DS), and number of tumors and size of the lesions at study inclusion and on last imaging prior to LT were not predictive of HCC recurrence on univariate analysis. The Kaplan-Meier 3-year post-LT probability of HCC recurrence was 26.0% for patients with an AFP ≥ 100 ng/mL compared with 12.7% for patients with an AFP < 100 (P = 0.03; Fig. 4).

TABLE 3. Univariate and Multivariable Analyses of Pre-LT Predictors of Post-LT Death Using Cox Proportional Hazards Regression Among Patients Ever Beyond Milan Criteria (n = 543)

Predictor	Hazard ratio (95% CI)	*P* Value
Univariate analysis		
Age (per year)	0.99 (0.96-1.02)	0.59
Tumor burden at study inclusion		
"AC-DS" (vs. "UNOS-DS")	1.26 (0.77-2.04)	0.35
Number of tumors (per tumor)	1.07 (0.88-1.30)	0.51
Total tumor diameter (per cm)	1.03 (0.94-1.13)	0.53
Number of tumors plus size of largest tumor (cm)	0.99 (0.88-1.11)	0.82
Last tumor burden prior to transplant		
Number of tumors (per tumor)	1.08 (0.85-1.38)	0.51
Total tumor diameter (per cm)	1.06 (0.98-1.14)	0.13
Number of tumors plus size of largest tumor (cm)	1.08 (0.996-1.17)	0.06
AFP at LT (ng/mL)		
AFP > 100 (vs <20)	2.37 (1.24-4.54)	0.009
AFP 20-99 (vs. <20)	1.53 (0.91-2.55)	0.11
MELD score (per point)	0.98 (0.93-1.03)	0.39
Wait region		
Mid (vs. long)	3.61 (1.64-7.96)	0.001
Short (vs. long)	2.49 (1.08-5.71)	0.03
Mid and short (vs. long)	3.12 (1.44-6.76)	0.004
Multivariable analysis		
AFP > 100 ng/mL (vs. <20)	2.36 (1.24-4.52)	0.009
AFP 20-99 ng/mL (vs. <20)	1.45 (0.87-2.43)	0.15
Mid and short wait region (vs. long)	3.07 (1.41-6.67)	0.005

VALIDATION OF RETREAT SCORE IN PATIENTS INITIALLY BEYOND MILAN CRITERIA

When combining patients in the UNOS-DS and AC-DS cohorts (n = 543), the observed 3-year probability of post-LT HCC recurrence was 4.5% in patients with a RETREAT score of 0-1, 13.4% with score of 2-3, and 44.2% for a score ≥4 (P < 0.001). RETREAT performed well in the down-staging

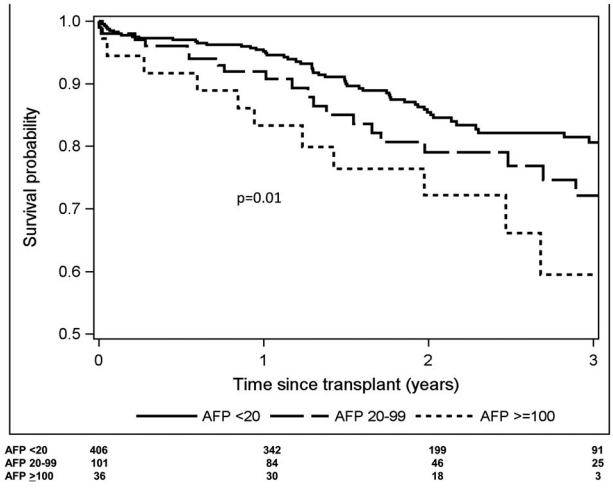

FIG. 3. Kaplan-Meier probability of post-LT survival in patients ever beyond Milan on pre-LT imaging (n = 543) stratified by AFP at LT.

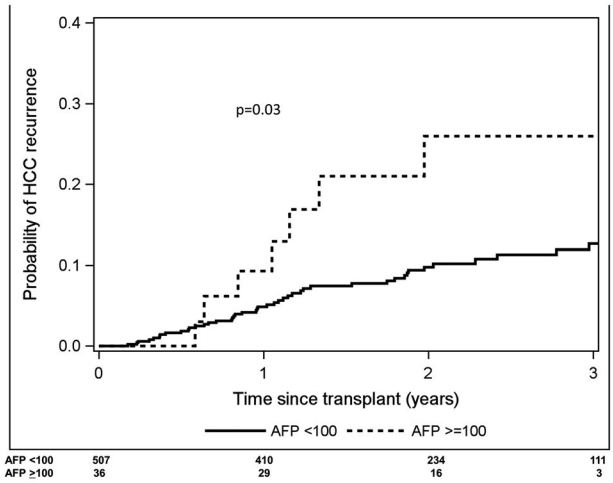

FIG. 4. Kaplan-Meier probability of post-LT recurrence in patients ever beyond Milan on pre-LT imaging (n = 543) stratified by AFP at LT.

groups with a C-index of 0.71 (95% CI, 0.64-0.78) for HCC recurrence prediction, superior to the Milan criteria by explant (C-index, 0.60; 95% CI, 0.52-0.68). The overall net reclassification index at 2 years after LT in patients initially beyond Milan criteria was 0.67 (P < 0.001), showing statistically significant improvement in recurrence risk classification for RETREAT compared with Milan criteria at explant. Risk classification was improved both among patients with HCC recurrence with net relative improvement of 26.9% (P = 0.03) and among patients without HCC recurrence (40.5%; P < 0.001). Among the down-staging groups, post-LT survival decreased with increasing RETREAT score. At 3 years after LT, observed survival was 89.4% for a RETREAT score of 0, 79.5% for a score of 2, 68.0% for a score of 3, and only 53.5% for a score ≥5 (P < 0.001).

Discussion

Once a highly contentious topic,[29] tumor down-staging has now emerged at the forefront of LT for HCC as a prognostication and selection tool. Down-staging represents a structured approach that aims at merging tumor morphologic parameters with objective and sustained response to LRT and is supported by the observation that post-LT survival outcomes in those who have been successfully down-staged to conventional Milan criteria are not significantly different compared with those who meet Milan criteria at presentation.[19] In the article by Mazzaferro aiming at "squaring the circle" of selection and allocation in LT for HCC,[30] the down-staged group was ranked in the highest priority category for LT allocation according to the assessments of highly complex principles of allocation and utility. Controversies persist, however, concerning both the optimal upper limits and targeted endpoint of tumor burden in down-staging, largely because there have been very scant data examining the effects of changing these boundaries on post-LT outcomes.[18]

In an effort to standardize criteria for down-staging of HCC prior to LT, UNOS recently adopted the UCSF/Region 5 down-staging protocol as a new national policy for granting automatic MELD exception for LT.[21] Even prior to the implementation of this new policy, many centers across different regions have already applied tumor down-staging but without standardized inclusion criteria.[21] This has also provided the opportunity to evaluate the national experience of tumor down-staging and compare the outcomes using UNOS-DS versus more liberal or even unrestricted inclusion criteria. In this study on the national experience of tumor down-staging using the UNOS database, we observed similar 3-year post-LT survival among patients with HCC always within Milan criteria (83%) compared with those

initially meeting UNOS-DS criteria (79%) who were successfully down-staged into Milan criteria prior to LT. In contrast, the 3-year post-LT survival in the AC-DS cohort with initial tumor burden exceeding UNOS-DS criteria was significantly lower at 71%. These findings based on the largest down-staging cohorts to date have validated the UNOS-DS criteria.

Despite optimism that stems from comparable post-LT survivals between the UNOS-DS and Milan groups, there are several notes of caution. We observed in the UNOS-DS cohort a relatively high proportion of patients with explant tumor stage beyond Milan criteria (33%), reflecting either pre-LT under-staging or inadequate response to down-staging, as well as a higher 3-year post-LT HCC recurrence rate of 13% in this group versus 7% in the Milan group. Samoylova et al. recently reported inaccuracies and biases in reporting tumor size by LT centers for patients meeting conventional LT criteria.[31] Adherence to the endpoint of down-staging to be within Milan criteria before LT and observing disease stability for at least 3 to 6 months are essential in minimizing the risks for tumor recurrence. We found that within the UNOS-DS group, those from SWR and MWR had significantly worse post-LT survival compared with LWR. The 3-year post-LT survival was 92% in LWR (median wait time of 12.8 months from MELD exception to LT), compared with only 73% in MWR (median wait time 6.5 months) and 79% in SWR (median wait time 2.6 months). In a multicenter down-staging study by Mehta et al. from Region 5,[20] a minimal observation of 3 months from successful down-staging to LT was required to ensure disease stability, but the actual period of observation was significantly longer at more than 12 months. These findings suggest an influence of longer wait time in selecting better candidates for LT after tumor down-staging. The 2015 UNOS policy for a mandatory delay of 6 months for all patients with HCC before granting listing priority[32] means that even in an SWR, a patient with tumors successfully down-staged would have sufficient time for observing durable response to down-staging before LT, thereby potentially eliminating the discrepancies in post-LT outcomes due to wait time differences.

Previous reports on down-staging were unable to identify predictors of post-LT HCC recurrence because of the limited number of recurrences and the relatively small overall sample size.[17-20] A major strength of the present study is the large sample size of the DS cohorts in the UNOS database (n = 543) to allow for robust analysis of pre-LT factors associated with post-LT HCC recurrence to refine selection criteria. In the multivariable model, AFP ≥ 100 ng/mL at LT (despite LRT) predicted inferior post-LT outcomes in the down-staging groups. The 3-year post-LT HCC recurrence rate was more than 25% and the 3-year post-LT survival was only 60% in the subgroup with AFP > 100 ng/mL at LT. In a French multicenter study by Duvoux et al., an AFP of >1,000 ng/mL among patients within Milan criteria was associated with worse post-LT survival, but a lower AFP cutoff of >100 ng/mL predicted inferior outcome among those with higher tumor burden beyond Milan criteria.[10] Another intriguing observation in the present study is that increased tumor burden on the last imaging study prior to LT (despite down-staging to within Milan criteria) was associated with explant tumor stage beyond Milan criteria. Specifically, the odds of being under-staged on explant increased by 10% for each 1-cm increase in total tumor diameter on this last imaging study. Taken together, in patients successfully down-staged to within Milan criteria, AFP ≥ 100 and radiographic tumor burden are important factors that help determine if a patient should undergo LT versus additional LRT. In the latter scenario, both biochemical response (AFP reduction) and radiographic response would be expected to further improve their post-LT outcome.

The results of the present study support using UNOS-DS criteria in the application of tumor down-staging on a broad scale and cast doubt on the benefits of down-staging in the "all-comers" group from the perspective of achieving acceptable post-LT outcomes. In addition to having the lowest 3-year post-LT survival, patients in the AC-DS group also had the highest probabilities of post-LT HCC recurrence at 3 years (16.7%), microvascular invasion (18%), and under-staging on explant to beyond Milan criteria (41%) compared with the UNOS-DS and Milan groups, despite having the lowest median AFP at the time of LT. In a single-center study by Rassiwala et al. from an LWR focusing on the intention-to-treat outcome under their AC-DS protocol,[33] increasing tumor burden predicted decreased probability of achieving successful tumor down-staging to within Milan criteria. The authors also found very low intention-to-treat survival of 21% at 5 years, and a very low LT rate of only 13% after successful tumor down-staging. Based on these observations as well as the inferior

post-LT outcomes in the current study when compared with the UNOS-DS group, there is a need for more stringent LT selection criteria for patients in the AC-DS group if these patients were to be considered for LT. This may partly already be in effect given the observation that patients in the down-staging groups had lower AFP both at baseline and prior to LT compared with the Milan group. Presumably, UNOS-DS and AC-DS patients with elevated AFP at baseline are less likely to be able to be down-staged (or have tumor progression after initial down-staging) and thus ultimately are excluded from LT. Perhaps implementing an even lower AFP cutoff before LT is needed for the AC-DS group to justify allocating organs to this group with considerable initial tumor burden and inferior post-LT outcome compared with the Milan and UNOS-DS groups. Specifically, of the 22 patients in the AC-DS cohort with an AFP at LT > 20 ng/mL, the 3-year probability of survival was only 50% and the 3-year probability of recurrence was 28%. Other considerations include mandating a longer period of stability before LT to select less aggressive tumors for LT to minimize HCC recurrence, setting an upper limit in tumor burden to have a realistic chance for achieving successful down-staging, and standardizing more stringent exclusion criteria for LT such as the development of new lesions during the period of observation.[33]

The present study has also validated the RETREAT score in predicting post-LT HCC recurrence in the down-staging populations. The RETREAT score was developed in a multicenter study[24] and was further validated in an analysis of the UNOS database[34] as a powerful clinicopathologic prognostic index primarily in patients meeting the Milan criteria before LT. Within the down-staging groups in the present study, increasing RETREAT scores predicted not only increased post-LT HCC recurrence (Harrell's C-index 0.71) but also worse post-LT survival. A RETREAT score of 0 was associated with a 3-year post-LT survival of nearly 90%, versus just over 50% for a RETREAT score of ≥5. RETREAT also demonstrated improved HCC recurrence prognostication compared with explant Milan criteria by both Harrell's C-Index and the net reclassification index.

There are several limitations of the present study. In relying on pretransplant tumor-related data supplied to UNOS by individual LT centers, some patients might have been misclassified into the Milan or UNOS-DS cohorts if tumor burden exceeding these criteria were not reported. Comparisons of post-LT survival and HCC recurrence by wait time regions within the AC-DS group were limited by the relatively small numbers in each wait time region. In addition, no mandate required LT centers to report HCC recurrence, and our aim to capture explant data (available only since April 2012) resulted in a relatively short median post-LT follow-up of 1.9 years, although similar post-LT follow-up was noted in the three cohorts (*P* values > 0.50). These factors could have resulted in underestimation of post-LT HCC recurrence. Consequently, we used post-LT survival as the primary outcome in this study. Additionally, we chose to analyze wait time region as a surrogate for individual wait time to LT because date of initial HCC diagnosis was not accurately recorded in the UNOS database, and this date could vary in relation to date of listing with MELD exception. Finally, all patients initially beyond Milan criteria who were down-staged into Milan presumably would have received LRT prior to LT, but LRT was not reported in 1.4% of the UNOS-DS and 3.3% of the AC-DS groups, respectively. These patients (n = 10 or 1.8% of the down-staging groups) were therefore incorrectly reported as not having received LRT or misclassified as having undergone down-staging.

In conclusion, in this study examining the national experience of LT after down-staging to Milan criteria, we found similar 3-year post-LT survival between the Milan and UNOS-DS groups but significantly worse survival in the AC-DS group. These results support the need for placing a restriction on the upper limits in tumor burden for down-staging and validate the inclusion criteria (UNOS-DS) in the national policy on down-staging recently implemented in 2017. We also found that shorter wait-list time and AFP ≥ 100 ng/mL at LT were associated with worse post-LT survival in the down-staging groups. These findings should frame future refinements to improve post-LT outcomes.

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