Impact of Pretransplant Bridging Locoregional Therapy for Patients With Hepatocellular Carcinoma Within Milan Criteria Undergoing Liver Transplantation

Analysis of 3601 Patients From the US Multicenter HCC Transplant Consortium

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Objective: To evaluate the effect of pretransplant bridging locoregional therapy (LRT) on hepatocellular carcinoma (HCC) recurrence and survival after liver transplantation (LT) in patients meeting Milan criteria (MC).

Summary Background Data: Pre-LT LRT mitigates tumor progression and waitlist dropout in HCC patients within MC, but data on its impact on post-LT recurrence and survival remain limited.

Methods: Recurrence-free survival and post-LT recurrence were compared among 3601 MC patients with and without bridging LRT utilizing competing risk Cox regression in consecutive patients from 20 US centers (2002–2013).

Results: Compared with 747 LT recipients not receiving LRT, 2854 receiving LRT had similar 1, 3, and 5-year recurrence-free survival (89%, 77%, 68% vs 85%, 75%, 68%; $P = 0.490$) and 5-year post-LT recurrence (11.2% vs 10.1%; $P = 0.474$). Increasing LRT number [3 LRTs: hazard ratio (HR) 2.1, $P < 0.001$; 4+ LRTs: HR 2.5, $P < 0.001$), and unfavorable waitlist alphafetoprotein trend significantly predicted post-LT recurrence, whereas LRT modality did not. Treated patients achieving complete pathologic response (cPR) had superior 5-year RFS (72%) and lower post-LT recurrence (HR 0.52, $P < 0.001$) compared with both untreated patients (69%; $P = 0.010$; HR 1.0) and treated patients not achieving cPR (67%; $P = 0.010$; HR 1.31, $P = 0.039$), who demonstrated increased recurrence compared with untreated patients in multivariate analysis controlling for pretransplant and pathologic factors (HR 1.32, $P = 0.044$).

Conclusions: Bridging LRT in HCC patients within MC does not improve post-LT survival or HCC recurrence in the majority of patients who fail to achieve cPR. The need for increasing LRT treatments and lack of alphafetoprotein response to LRT independently predict post-LT recurrence, serving as a surrogate for underlying tumor biology which can be utilized for prioritization of HCC LT candidates.

Keywords: HCC recurrence, hepatocellular carcinoma, liver transplantation, locoregional therapy, recurrence-free survival

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Liver transplantation (LT) has unequivocally been established as the gold-standard, curative-intent therapy for patients with unresectable hepatocellular carcinoma (HCC), meeting the specified radiological Milan size criteria.[1] Given ongoing concerns with overprioritization of HCC recipients compared with noncancer patients with end-stage liver disease,[2–4] there have been continuous refinements to the Organ Procurement and Transplantation Network (OPTN) policy for granting model for end-stage liver disease (MELD) exception points to HCC LT recipients. The most recent modification in October of 2015 instituted a requirement for a mandatory 6-month waiting period before awarding 28 MELD exception points, and a capping of the MELD score at 34 for HCC recipients with preserved underlying liver function.[5]

With an increase in the anticipated wait-times across all United Network for Organ Sharing (UNOS) regions, it is expected that pretransplant locoregional therapy (LRT) will be universally utilized across all transplant centers to mitigate the inherent risk of tumor progression and waitlist dropout, in accordance with a recent international consensus statement regarding the waitlist management of HCC patients.[6] Numerous studies support that pre-LT LRT procedures such as transarterial chemoembolization (TACE)[7–10] and percutaneous thermal ablative strategies [radiofrequency ablation (RFA), microwave ablation (MWA)][11,12] mitigate waitlist dropout by achieving tumor necrosis, the presence of which may be estimated by preoperative radiological[13–19] and serum alphafetoprotein (AFP) responses to LRT.[20,21] However, the effectiveness of bridging LRT on improving post-LT recurrence and survival appear to be limited to patients who achieve a robust complete pathologic response most definitively evaluated on explant pathology.[22,23]

Without any prospective studies to compare the relative effectiveness of different bridging LRTs on reducing post-LT recurrence and improving survival; existing data have mostly been limited to retrospective, single-center experiences of limited sample sizes to adequately address these questions. With our large, national, multicenter consortium database of 3601 patients with tumors within Milan criteria (MC), we sought to evaluate the effect of LRT modality, number, and AFP response to treatment on post-LT HCC recurrence and survival.

METHODS

The US Multicenter HCC Transplant Consortium (UMHTC) was initiated in January of 2015 to develop and maintain a database of patients with HCC undergoing LT, and consists of 20 contributing academic transplant centers encompassing 10 of the 11 UNOS regions (Supplementary Digital Content Figure, http://links.lww.com/SLA/B275). The consortium database inclusion criteria included all consecutive, adult (aged 18 years or more) patients with HCC undergoing LT from 2002 to 2013 regardless of tumor size, requirement for MELD exception points, follow-up time, or non-HCC-related death. The diagnosis of HCC was based on pretransplant radiographic imaging [Organ Procurement and Transplantation Network (OPTN) 5B criteria], biopsy, or incidental discovery on explant pathology. Patients with cholangiocarcinoma, mixed hepatocellular/cholangiocarcinoma, fibrolamellar HCC, or hepatoblastoma were excluded. The study was approved by each transplant centers' institutional review board, and data were collected, deidentified, and stored in a password-encrypted central database managed by the UMHTC at the University of California, Los Angeles.

The primary objective of this project was to examine the impact of bridging pretransplant LRT on post-LT HCC recurrence and survival; hence, analysis was limited to the subset of LT recipients with a known pre-LT diagnosis of HCC meeting the radiological MC, with exclusion of recipients whose tumors were beyond the MC or with incidental HCC on explant. Variables analyzed included age, sex, underlying liver disease, laboratory and match MELD (includes exception points) at time of transplantation, radiographic size criteria, maximum and immediate pretransplant serum AFP, pretransplant neutrophil-lymphocyte ratio (NLR), total cholesterol, and receipt of LRT. LRT included both the total number of treatments and modality, with TACE and thermal ablation (radiofrequency or microwave ablation) the most predominant treatments. For purposes of analysis, recipients were categorized into 4 groups: TACE, without ablation; ablation, without TACE; TACE and ablation; and other (including transarterial radioembolization, percutaneous ethanol ablation, surgical resection, cryoablation, and radiation-based therapies). Explant pathologic variables included total tumor number, maximum tumor diameter, grade/differentiation, and presence of microvascular and macrovascular invasion. LT recipients with no viable tumor after LRT were categorized as having a complete pathologic response (cPR). Patient-specific follow-up included time to post-transplant HCC recurrence or death, with all LT recipients characterized at last follow-up as alive, alive with recurrence, dead due to recurrence, or dead not related to HCC recurrence.

Statistical Analysis

Covariates were compared among groups with and without pre-LT LRT using the Wilcoxon rank-sum test (continuous variables) or the Fisher/chi-square test (categorical variables). Recurrence-free survival (RFS) curves were constructed using the Kaplan–Meier method and compared across specified groups using the log-rank test, whereas recurrence incidence curves were constructed and compared using Gray method, taking into account the competing risk of non-HCC-related mortality.

We evaluated the relationship between receipt of LRT, and also LRT modality and number of treatments with the post-LT rate of HCC recurrence using the Fine and Gray regression model, taking into account the competing risk of non-HCC recurrence-related mortality before and after adjusting for known pretransplant covariates. In a separate analysis, the relationship between LRT status and the rate of recurrence for the subset of patients who did not achieve cPR was evaluated using a similar model with and without adjustment for pretransplant and post-transplant factors. The variables for maximum AFP, immediate pre-LT AFP, NLR, and pathologic maximum diameter were skewed on the original scale, and were thus log-transformed for the purpose of the analyses since the log-transformed values approximated a normal distribution. Linearity was assessed by fitting splines. The proportional-hazards assumption was evaluated using Schoenfeld residuals. Final models were selected using the backwards procedure for variable selection and liberal $P < 0.25$ as the retention criterion. Missing values were singly imputed for the purpose of the multivariable analysis using Markov Chain Monte Carlo regression imputation.

RESULTS

Of 3601 patients in the UMHTC with a known pre-LT diagnosis of HCC meeting MC, 2854 (79.3%) received pre-LT LRT, whereas 747 (20.7%) did not. At a median follow-up time of 46.7 months [interquartile range (IQR) 24.2–76.2], 375 patients developed post-LT HCC recurrence (10.4%) with a median time to recurrence of 17.2 months (IQR 8.5–34.1). At time of last follow-up, 2433 (67.6%) were alive without recurrence, 95 (2.6%) had recurred but were alive, 279 (7.7%) had died of HCC recurrence, and 794 (22.1%) had non-HCC-related mortality.

The distribution of pretransplant locoregional treatment modality and number is shown in Table 1. Of 3601 HCC LT recipients, 747 (20.7%) received no LRT, 1922 (53.4%) received TACE and not

TABLE 1. Distribution of Pretransplant Locoregional Treatment Modality and Number

	N	%
LRT modality		
None	747	20.7
TACE, not ablation	1922	53.4
Thermal ablation, not TACE	464	12.9
TACE and thermal ablation	298	8.3
Other	170	4.7
Radioembolization (Y-90)	58	1.6
Ethanol ablation	46	1.3
Surgical resection	35	1.0
Cryoablation/chemical ablation	10	0.2
Radiation	3	0.1
Miscellaneous	18	0.5
Number of treatments		
0	747	20.7
1	1820	50.5
2	655	18.2
3	223	6.2
4	91	2.5
5	42	1.2
6+	23	0.7
LRT modality and number		
None	747	20.7
TACE/1 treatment	1294	35.9
TACE/2 treatments	408	11.3
TACE/3+ treatments	220	6.1
Thermal ablation/1 treatment	381	10.6
Thermal ablation/2 treatments	63	1.8
Thermal ablation/3 treatments	20	0.6
TACE and thermal ablation/2 treatments	166	4.6
TACE and thermal ablation/3+ treatments	132	3.7
Other	170	4.7
Number of treatments by UNOS region*		
0		
Short wait time (3, 10)	95	19.5
Medium wait time (2, 4, 7, 8, 11)	398	24.9
Long wait time (1, 5, 9)	254	16.8
1		
Short wait time (3, 10)	320	65.6
Medium wait time (2, 4, 7, 8, 11)	899	56.2
Long wait time (1, 5, 9)	601	39.8
2+		
Short wait time (3, 10)	73	14.9
Medium wait time (2, 4, 7, 8, 11)	304	18.9
Long wait time (1, 5, 9)	657	43.4

*P value <0.001 comparing number of treatments across 3 different wait-time regions.

thermal ablation, 464 (12.9%) received ablation without TACE, 298 (8.3) received both TACE and ablation, and 170 recipients received other LRT without TACE or ablation (4.7%). Regarding number of total pretransplant treatments, the majority received 1 LRT (n = 1820, 50.5%), with 655 (18.2%), 223 (6.2%), 91 (2.5%), 42 (1.2%), and 23 (0.7%) receiving 2, 3, 4, 5, and 6 or more treatments, respectively. Evaluation of LRT practices across UNOS regions comparing short (regions 3, 10), medium (regions 2, 4, 7, 8, 11), and long-wait time regions (1, 5, 9) demonstrated that patients in long wait-time regions required significantly greater number of treatments and were less likely to not receive treatment compared with recipients in medium and short wait-time regions ($P < 0.001$; Table 1).

Demographic, laboratory, and explant pathologic variables are shown in Table 2. Compared with patients not receiving LRT, recipients with pre-LT LRT were older (59 vs 56, $P < 0.001$); more likely to have hepatitis B virus (11.5% vs 7.8%; $P = 0.004$); had lower median laboratory MELD scores (12 vs 17; $P < 0.001$) and NLR (2.7 vs 3.3; $P < 0.001$); greater median match MELD (25 vs 24; $P < 0.001$), pre-LT maximum AFP (21 vs 15; $P < 0.001$), and total cholesterol (141 vs 137; $P = 0.008$); and on explant pathology were more likely to have greater number of tumors ($P = 0.007$), greater maximum tumor diameter (2.5 vs 2.3 cm; $P < 0.001$), greater cPR/no viable tumor (24.6% vs 4.8%; $P < 0.001$), and less likely to have microvascular (16.8% vs 22.8%) and macrovascular (3.4% vs 5.1%; $P < 0.001$) invasion. Despite differences in demographic, laboratory, and explant pathologic variables, recipients receiving LRT had a similar 1, 3, and 5-year RFS compared with patients not receiving LRT (89%, 77%, 68% vs 85%, 75%, 68%; $P = 0.490$; Fig. 1A), with no difference in the 5-year cumulative incidence of recurrence (11.2% vs 10.1%; $P = 0.474$; Fig. 1B).

Survival and Recurrence Outcomes

When stratified by LRT modality, there were no significant differences in the 1, 3, and 5- year RFS among patients not receiving LRT, or receiving TACE, ablation, TACE and ablation, or other modalities (Fig. 2A), with a minimal, nonsignificant range in 5-year RFS from highest (69%—ablation group) to lowest (65%—TACE and ablation; $P = 0.527$). Conversely, the number of treatments significantly affected RFS (Fig. 2B), with the lowest 5-year survival observed in recipients receiving 3 (63%) and 4 or more (51%) treatments compared with recipients receiving 0, 1, or 2 treatments ($P < 0.001$).

When controlling for the competing risk of non-HCC mortality, 5-year cumulative recurrence incidence did not vary significantly when stratified by LRT modality (Fig. 2C), with similar hazard ratios (HRs) for the majority of patients receiving TACE (HR 1.08, $P = 0.589$), ablation (HR 0.86, $P = 0.474$), and other modalities (HR 1.30, $P = 0.310$) compared with no LRT, with a slight increase in risk for patients receiving both TACE and ablation (HR 1.52, $P = 0.036$). However, HCC LT recipients demonstrated a greater incidence of recurrence with increasing number of LRTs, particularly patients receiving 3 (HR 2.1, $P < 0.001$) and 4 or more treatments (HR 2.5, $P < 0.001$) compared with patients not receiving LRT (Fig. 2D).

Similarly, the pretransplant AFP change/response to LRT from the maximum pretransplant value to the immediate pretransplant value was predictive of HCC recurrence, with the lowest HR observed for HCC recipients who never demonstrated an AFP >20 (pre-LT AFP = max, but normal <20; HR 1.0) and patients whose pre-LT maximum AFP was greater than 20, but completely normalized to <20 (HR 0.9, $P = 0.603$), with increased recurrence for LT recipients who did not normalize the AFP before LT (pre-LT AFP < max, improving but >20; HR 2.0, $P < 0.001$), and highest recurrence for LT recipients with increasing AFP levels before LT (pre-LT AFP = max, and high >20; HR 3.1 $P < 0.001$; Fig.s 2E).

A subset survival analysis to evaluate the impact of achieving cPR to pretransplant LRT is shown in Fig. 3. LT recipients receiving LRT and achieving cPR had significantly superior 5-year RFS (72% vs 69% and 67%, respectively; $P = 0.010$; Fig. 3A) and disease-specific survival (96% vs 91% and 89%, respectively; $P < 0.001$; Fig. 3B), and also a significantly reduced 5-year incidence of recurrence (HR 0.52, $P < 0.001$) compared with both patients not receiving LRT, and also recipients receiving LRT, but not achieving cPR (Fig. 3C). Interestingly, recipients receiving LRT and not achieving cPR demonstrated an increased risk of recurrence compared with patients not receiving LRT at all (HR 1.31, $P = 0.039$; Fig. 3C). In the subset of 702 recipients with cPR, the vast majority received 2 or fewer treatments (n = 636, 90.6%), with only a minority receiving 3 or more LRT (n = 66, 9.4%). Recipients with cPR receiving 3 or more treatments had a significantly greater incidence of post-LT recurrence (n = 10, 15.2%) compared with cPR recipients receiving 2 or fewer treatments (n = 25, 3.9%).

TABLE 2. Comparison of Characteristics Among HCC Liver Transplant Recipients With and Without Pretransplant Locoregional Therapy

	Overall (N = 3601)	No LRT (n = 747)	LRT (n = 2854)	*P*
Demographics				
Age, median (IQR)	58 (54–63)	56 (52–62)	59 (54–64)	<0.001
Male, %	75.9	75.9	75.9	0.988
Diagnosis, %				0.004
Hepatitis C	63.9	62.1	64.3	
Alcoholic liver disease	9.9	12.9	9.1	
Hepatitis B	10.7	7.8	11.5	
NASH	5.9	7.1	5.6	
Cryptogenic	3.7	3.9	3.7	
PBC/PSC	2.0	2.5	1.9	
Laboratory parameters, median (IQR)				
Laboratory MELD	13 (9–18)	17 (12–24)	12 (9–17)	<0.001
Transplant Match MELD	25 (22–28)	24 (22–28)	25 (22–28)	<0.001
Pre-LT maximum AFP	19 (7–93)	15 (6–59)	21 (8–107)	<0.001
Immediate pre-LT AFP	10 (5–36)	10 (5–42)	10 (5–35)	0.961
Neutrophil-lymphocyte ratio	2.9 (1.8–4.8)	3.3 (2.1–6)	2.7 (1.8–4.5)	<0.001
Total cholesterol	140 (114–167)	137 (105–166)	141 (116–167)	0.008
Explant pathology				
Number of tumors, %				0.007
1	50.3	54.9	49.1	
2	22.8	22.8	22.8	
3	10.8	10.2	11.0	
4	4.6	4.6	4.7	
5+	6.9	5.6	7.3	
Maximum tumor diameter, cm, median (IQR)	2.5 (1.7–3.5)	2.3 (1.7–3.1)	2.5 (1.8–3.5)	<0.001
Differentiation, %				<0.001
Well	22.7	28.8	21.1	
Moderate	46.3	53.8	44.0	
Poor	8.2	11.1	7.5	
cPR/no viable tumor	20.5	4.8	24.6	
Vascular invasion, %				<0.001
None	77.6	71.9	79	
Microvascular	18.0	22.8	16.8	
Macrovascular	3.7	5.1	3.4	
AJCC T stage, %				0.017
T1	46.1	45.1	46.3	
T2	46.0	47.5	45.6	
T3a	3.4	2.0	3.7	
T3b/T4	3.7	5.1	3.4	

NASH indicates nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis response.

Univariate and Multivariate Analysis of LRT Modality and Number on Post-LT Recurrence

The effect of LRT modality and number of treatments on post-LT HCC recurrence is shown in Table 3. On univariate analysis controlling only for LRT modality, increasing number of treatments were consistently associated with increased risk of recurrence in patients receiving TACE (2 LRT: HR 1.50, $P = 0.025$ and 3+ LRT: HR 2.56, $P < 0.001$), ablation (3+ LRT: HR 5.25, $P < 0.001$), and TACE and ablation (3+ LRT: HR 1.93, $P = 0.043$). However, controlling for the total number of LRTs, there was no difference in post-LT recurrence when comparing patients with TACE, ablation, or the combination of treatments in patients receiving 1, 2, or 3, or

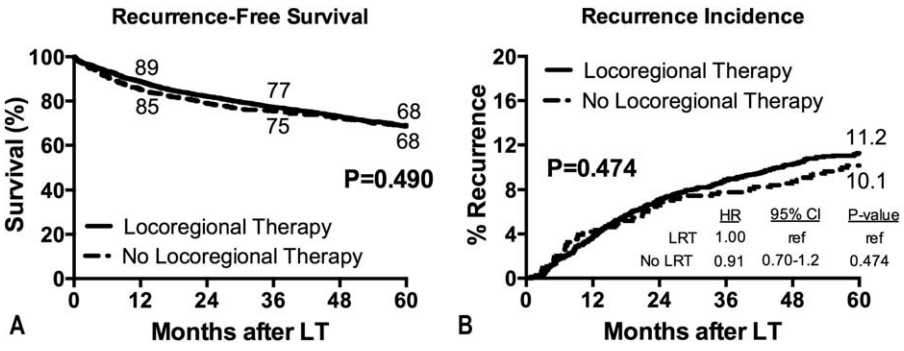

FIGURE 1. Kaplan–Meier recurrence-free survival (A) and cumulative incidence of recurrence controlled for competing risk of non-HCC mortality (B) comparing HCC recipients with and without pretransplant LRT.

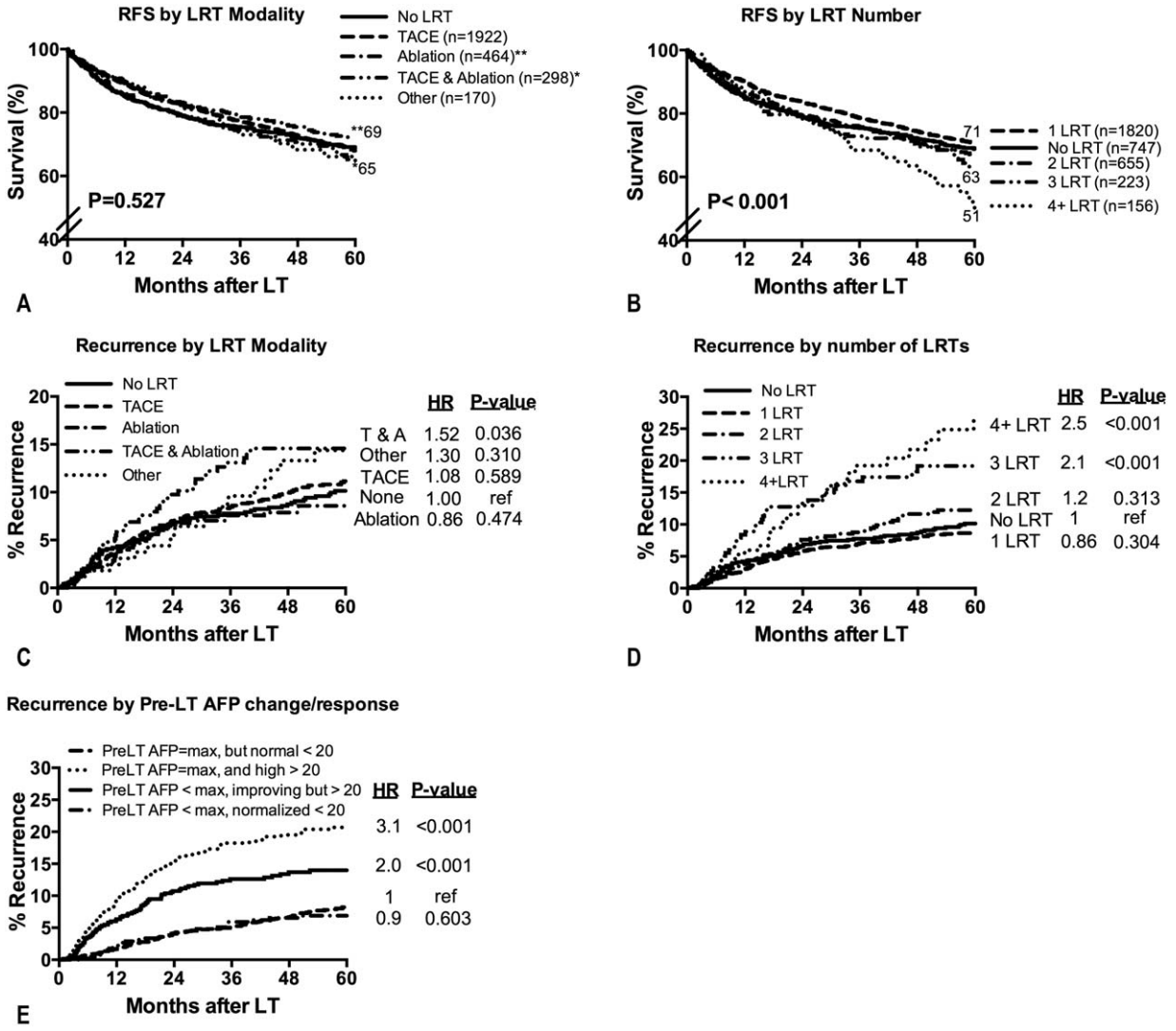

FIGURE 2. Kaplan–Meier recurrence-free survival of 3601 HCC recipients undergoing liver transplantation after pretransplant locoregional tumor treatment stratified by (A) locoregional therapy modality and (B) locoregional therapy number, and also cumulative incidence of HCC recurrence controlled for the competing risk of non-HCC mortality stratified by (C) LRT modality, (D) number of LRT treatments, and (E) AFP response/change over the waitlist period. T&A, TACE and ablation.

more LRTs. Even after controlling for other knowable pretransplant prognostic factors such as AFP and NLR in multivariate analysis, increasing number of pre-LT treatments continued to portend increased post-LT HCC recurrence among recipients receiving TACE (2 LRTs: HR 1.46, $P = 0.053$ and 3+ LRTs: HR 2.58, $P < 0.001$), ablation (3+ LRTs: HR 2.58, $P < 0.001$), and TACE and ablation (3+ LRTs: HR 1.97, $P = 0.060$). However, similar to univariate analysis, multivariate analysis revealed that LRT modality did not impact post-LT recurrence when controlled for the total number of LRTs, AFP, and NLR.

Finally, a subset multivariate analysis to examine our finding that post-LT HCC recurrence was increased in patients receiving LRT and not achieving cPR compared with patients not receiving LRT at all (Fig. 3C) is shown in Table 4. Even after controlling for pretransplant diagnosis, MELD, AFP, and prognostic pathologic factors (pathologic maximum tumor diameter, differentiation, and vascular invasion), LT recipients receiving LRT and not achieving cPR had a significantly greater rate of recurrence compared to patients not receiving LRT [HR 1.32, 95% confidence interval (CI) 1.01–1.72, $P = 0.044$]. In this multivariate analysis, further analysis of the impact of receiving LRT and not achieving cPR was evaluated by examining mutually exclusive groups stratified by LRT type and number. Once again, the need for 3 or more LRTs was independently predictive of increased post-LT HCC recurrence in patients receiving TACE (HR 2.06, 95% CI 1.37–3.09, $P = 0.001$), ablation (HR 5.02, 95% CI 2.44–10.3, $P < 0.001$), and TACE and ablation (HR 1.82, 95% CI 1.09–3.04, $P = 0.023$).

DISCUSSION

Despite growing evidence highlighting the importance of HCC tumor response to pretransplant LRT for unresectable HCC patients awaiting LT,[17] MELD exception points continue to be

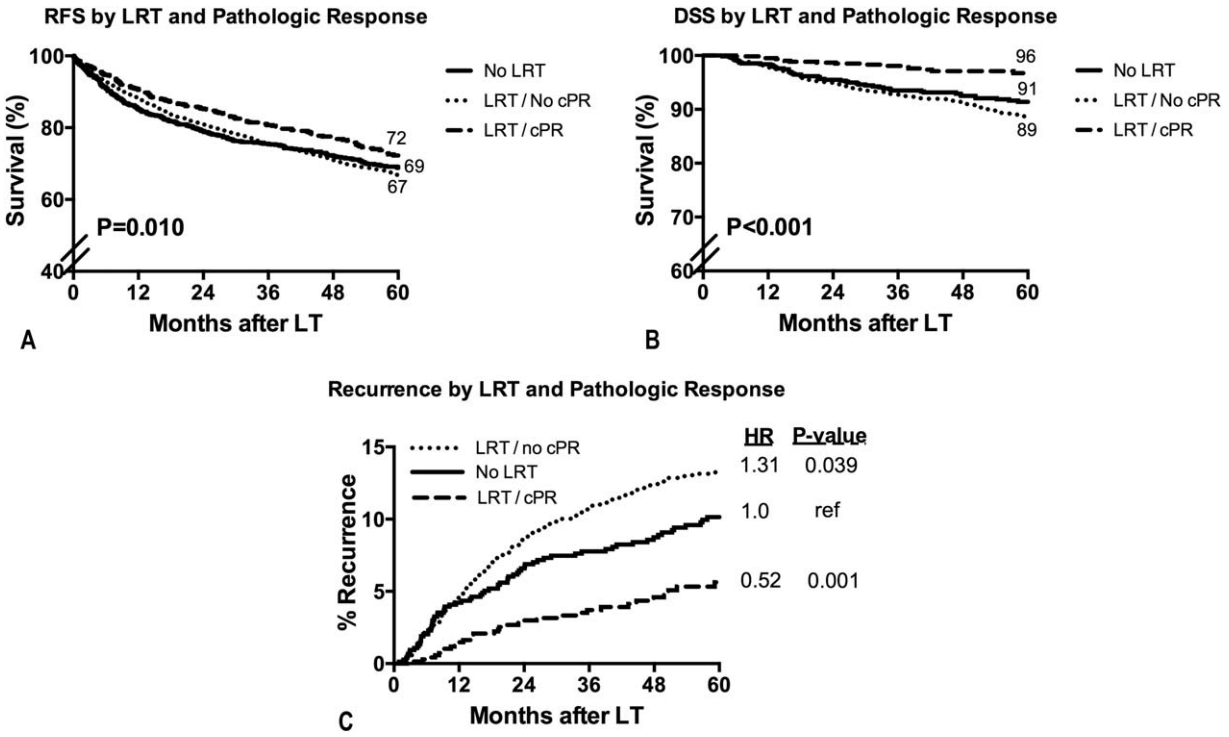

FIGURE 3. Kaplan–Meier recurrence-free survival (A), disease-specific survival (B), and cumulative incidence of HCC recurrence controlled for the competing risk of non-HCC mortality (C) in HCC patients undergoing LT with comparison of patients receiving LRT and achieving cPR, receiving LRT and not achieving cPR, and not receiving LRT.

granted in accordance with a uniform policy that does not yet take into consideration dynamic evaluations of an individual's tumor biology over the course of their treatment before LT. With recent policy changes mandating a 6-month waiting period before granting MELD exception points,[5] it is anticipated that most HCC patients with enough functional liver reserve will undergo pretransplant LRT to mitigate waitlist dropout. As such, a robust analysis of the impact of bridging LRT on post-LT outcomes is critical. With granular data

TABLE 3. Univariate and Multivariate Analysis Evaluating Effect of Locoregional Modality and Number on Posttransplant HCC Recurrence

Univariate Analysis					Multivariate Analysis*				
Controlled Factor	**Variable**	**HR**	**95% CI**	***P***	**Controlled Factor**	**Variable**	**HR**	**95% CI**	***P***
TACE	1 LRT	ref	—	—	TACE	1 LRT	ref	—	—
	2 LRT	1.50	1.05–2.14	0.025		2 LRT	1.46	0.99–2.13	0.053
	3+ LRT	2.56	1.77–3.71	<0.001		3+ LRT	2.58	1.75–3.79	<0.001
Ablation	1 LRT	ref	—	—	Ablation	1 LRT	ref	—	—
	2 LRT	0.91	0.32–2.62	0.866		2 LRT	0.89	0.30–2.59	0.826
	3+ LRT	5.25	2.11–13.0	<0.0001		3+ LRT	5.60	2.32–13.5	<0.001
TACE and ablation	2 LRT	ref	—	—	TACE and ablation	2 LRT	ref	—	—
	3+ LRT	1.93	1.02–3.66	0.043		3+ LRT	1.97	0.97–4.00	0.060
1 LRT	TACE	ref	—	—	1 LRT	TACE	ref	—	—
	Ablation	0.89	0.57–1.37	0.582		Ablation	1.05	0.67–1.64	0.833
2 LRT	TACE	ref	—	—	2 LRT	TACE	ref	—	—
	Ablation	0.54	0.19–1.50	0.237		Ablation	0.64	0.22–1.82	0.401
	Ablation and TACE	0.85	0.48–1.51	0.580		Ablation and TACE	0.84	0.44–1.59	0.587
3+ LRT	TACE	ref	—	—	3+ LRT	TACE	ref	—	—
	Ablation	1.81	0.75–4.38	0.186		Ablation	2.28	0.97–5.36	0.059
	Ablation and TACE	0.96	0.57–1.61	0.882		Ablation and TACE	0.93	0.54–1.60	0.798
					Pre-LT AFP†		2.01	1.77–2.30	<0.001
					Pre-LT NLR†		1.53	1.15–2.03	0.003

*Multivariate analysis controls for pretransplant factors including AFP and NLR.
†Hazard ratios for AFP and NLR reported per log unit increase.

TABLE 4. Multivariate Analysis of LRT Modality and Number on HCC Recurrence in Subset of LT Recipients Not Achieving cPR

	HR	95% CI	P
Group (in aggregate)			
No LRT	1.00	ref	ref
LRT/no cPR	1.32	1.01–1.72	0.044
Group (by modality and number)			
No LRT	1.00	ref	ref
TACE/1 LRT	1.18	0.87–1.62	0.291
TACE/2 LRT	1.32	0.87–2.00	0.188
TACE/3+ LRT	2.06	1.37–3.09	0.001
Ablation/1 LRT	1.08	0.67–1.72	0.756
Ablation/2 LRT	0.87	0.32–2.36	0.779
Ablation/3+ LRT	5.02	2.44–10.3	<0.001
TACE and ablation/2 LRT	1.29	0.74–2.25	0.362
TACE and ablation/3+ LRT	1.82	1.09–3.04	0.023
Other	1.24	0.70–2.18	0.461
Covariate			
Diagnosis			
Hepatitis B	1.00	ref	ref
Hepatitis C	0.85	0.59–1.23	0.396
Alcohol	1.03	0.64–1.66	0.888
NASH	0.76	0.42–1.38	0.367
Cryptogenic	0.50	0.22–1.10	0.086
PBC/PSC	0.36	0.09–1.51	0.162
Laboratory MELD (per unit)	1.01	1.00–1.03	0.114
Pre-LT AFP (per log unit)	1.51	1.32–1.73	<0.001
Pathologic maximum diameter (per log unit)	1.71	0.92–3.16	0.088
Pathologic tumor differentiation			
Well	1.00	ref	ref
Moderate	1.18	0.87–1.60	0.285
Poor	2.00	1.38–2.91	<0.001
Vascular invasion			
None	1.00	ref	ref
Microvascular invasion	2.25	1.76–2.88	<0.001
Macrovascular invasion	3.60	2.48–5.21	<0.001

NASH indicates nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

available from the US Multicenter HCC Transplant Consortium, we report the largest analysis of the impact of LRT modality, number, and AFP response to therapy in HCC patients undergoing LRT before LT.

In keeping with prior single-center studies and consensus statements,[6,24] results from our large consortium did not support any survival benefit for any particular LRT modality. Whether treated with TACE, thermal ablation, a combination of both, or other modalities, the 5-year RFS after LT was similar to and no different from the 20% of patients not receiving any LRT at all. Similarly, the post-transplant recurrence incidence controlling for the competing risk of non-HCC mortality demonstrated no reduction in post-LT HCC recurrence; in fact, LT recipients receiving both TACE and ablation appeared to have a 52% higher rate of recurrence compared with patients not receiving any therapy. This finding was not concordant with several other single-center experiences reporting an improvement in the rates of pathologic tumor response in patients receiving combination therapy, which in turn were associated with reduced recurrence.[22,25] In our study, it was not possible to definitively determine whether patients receiving combination therapy were strategically having the same tumor targeted, or whether a different LRT modality was used to address a treatment failure or a second de novo lesion. Hence, conclusions regarding the effectiveness of combination therapy on a single lesion cannot be made.

However, an objective finding not subjected to this same retrospective bias was the fact that the need for an increasing number of LRT treatments indisputably portended inferior outcomes. LT recipients requiring 3 or more treatments consistently demonstrated inferior 5-year RFS and an increased risk of post-LT recurrence compared with patients receiving 2 or fewer treatments. Even after univariate analysis controlling for LRT modality, and also multivariate analysis controlling for pretransplant surrogates of tumor biology (AFP and NLR), an increasing number of treatments was associated with increased recurrence across all LRT modalities and combinations (Table 3)—a finding contradicting past reports from smaller, single-center studies that reported no association of increasing TACE treatments with inferior outcomes.[26] Whereas radiologic assessments after LRT (modified response evaluation criteria in solid tumors)[16] were not available in our consortium dataset, the only reasonable conclusion is that interval imaging continued to show either persistent, progressing, or de novo viable lesions that prompted additional LRT in these patients. The radiologic response to LRT has widely been advocated as a useful pretransplant measure of tumor biology, with failure to respond to LRT portending increasing waitlist dropout, post-transplant recurrence, and inferior post-transplant survival.[10,14,18,20,27,28] Similarly, we contend that the need for an increasing number of LRTs is undoubtedly due to a persistent or de novo viable lesion. Thus, an increasing need for LRT, as a seemingly important surrogate for more aggressive tumor biology, may be incorporated into selection criteria to more accurately stratify post-transplant HCC recurrence risk compared with the current number and size criteria alone.

Serum AFP has been shown to not only correlate to radiographic responses to LRT,[29] but is itself an important dynamic marker of aggressive tumor biology.[22,30,31] In an analysis of 6817 HCC patients from the Scientific Registry of Transplant Recipients database, Merani et al[21] reported that a reduction of serum AFP to $\leq$400 ng/mL before LT was associated with a reduction in waitlist dropout and improved post-transplant survival comparable with patients with low AFP levels throughout their waitlist period. Lai et al[20] recently reported that an AFP slope increase of >15 ng/mL per month was an independent predictor of HCC recurrence and death in HCC patients undergoing LRT both within and beyond the MC. Our consortium findings add to the body of evidence arguing for the inclusion of dynamic AFP changes in prioritization of HCC patients for liver transplantation. Recipients with elevated AFP levels who were treated with LRT and normalized to AFP <20 before LT had similar risks of HCC recurrence compared with patients with normal AFP throughout their waitlist period, consistent with a recent study demonstrating better prognosis for LT patients with non-AFP-producing tumors.[32] LT recipients demonstrating a decrease in pre-LT AFP, but not yet normalizing their AFP before LT (pre-LT AFP < max, but still abnormal >20) had increased risk of post-LT HCC recurrence, with the highest HCC recurrence risk observed in patients who had increasing AFP levels before LT, despite receiving LRT (pre-LT AFP = max and >20). With this consortium data that can be generalized to all HCC recipients across the country, it is becoming increasingly clear that a dynamic evaluation of AFP response to LRT should be considered for HCC LT prioritization.

A unique strength of our database is the availability of detailed explant pathologic data. Whereas the use of LRT did not improve recurrence or survival compared with patients not receiving LRT when considering all patients, the subset of LT recipients receiving LRT and demonstrating a complete pathologic response without viable tumor had significantly superior RFS, disease-specific survival, and reduced HCC recurrence compared with both untreated patients and HCC patients receiving LRT, but not achieving cPR (Fig. 3A–C). The finding that LT recipients with cPR have improved outcomes has previously been reported, with numerous studies

demonstrating decreased recurrence and improved survival when LRT achieves cPR.[14,22,23,33,34] Perhaps more intriguing was our finding that patients receiving LRT and not achieving cPR had, in fact, worse outcomes compared with HCC patients not receiving any LRT at all. To assure that this phenomenon was not a result of comparing groups with varying patient and tumor characteristics, we performed a multivariate analysis controlling for important pretransplant (diagnosis, MELD, AFP) and pathologic (tumor diameter, differentiation, vascular invasion) characteristics. Even after controlling for these characteristics, HCC patients receiving LRT and not achieving cPR had an independently increased rate of HCC recurrence compared with patients not receiving LRT (HR 1.32, $P = 0.044$; Table 4), especially in the subset of patients receiving 3 or more treatments regardless of modality. To our knowledge, this is the first study specifically controlling for multiple prognostic factors to find that LRT itself may independently predict inferior outcomes in the subset of patients not achieving cPR. At a minimum, we can conclude that the need for increasing treatments may reflect an aspect of tumor biology that is not captured by the well-characterized laboratory markers and explant pathologic characteristics. A different and perhaps more contentious explanation may be that in a subset of patients, LRT itself may potentially be responsible for unmasking a more aggressive tumor behavior than if the lesion was left untouched, with some reports demonstrating increased cancer stem cell markers in tumors treated by TACE.[35] Without a priori knowledge of which patients receiving LRT will achieve cPR, we certainly cannot endorse the conclusion that some HCC patients should not receive treatment; nonetheless, our findings should prompt the liver cancer community to further examine the biological underpinnings of this intriguing phenomenon.

CONCLUSIONS

In summary, we report a national, multicenter consortium database analysis of the impact of pretransplant LRT on post-transplant recurrence and survival in patients with HCC within MC undergoing liver transplantation. The use of LRT results in improved survival and reduced recurrence only in the smaller subset of patients who achieve cPR, an unknowable characteristic before examination of the explant. We find no evidence to support the use of one locoregional modality over another; however, it is unequivocal that the need for an increasing number of LRTs, and also unfavorable AFP response to LRT are strong surrogates for aggressive underlying tumor biology that portend inferior outcomes. In fact, in recipients receiving LRT and not achieving cPR, the need for increasing LRT is an independent predictor of adverse outcomes even after controlling for patient demographic, laboratory, and pathologic characteristics, and may signal treatment resistance. With this study, we add highly valuable and generalizable data that supports the growing body of evidence that a static HCC MELD allocation policy that only takes into account tumor size and number fails to account for the variable risks of tumor progression, waitlist dropout, and post-transplant recurrence and survival. Incorporation of response to LRT, as assessed by radiologic response, need for increasing LRTs, and dynamic AFP changes are clear surrogates for tumor biology. How and when these factors will be incorporated into allocation policy, and what absolute risk of HCC recurrence will be considered prohibitive for liver transplantation, is up to our transplant community to decide.

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DISCUSSANTS

Dr K.M. Olthoff (Philadelphia, PA):

Dr Agopian and members, I thank you for the privilege to discuss this manuscript and for the opportunity to review the paper before the meeting. I have one small conflict in that one of our faculty did participate in submitting some of our patients to this study.

First, I would like to congratulate the authors and to acknowledge that this is the largest study to date evaluating the utilization of locoregional therapy before transplant as it relates to pathological and clinical outcomes in patients who have received a transplant for HCC within Milan criteria. The fact that it incorporates data from 20 centers, in 10 out of 11 UNOS regions, makes it much more representative of clinical outcomes and practice across the country than other previous, smaller studies, and serves as potential for future studies from this extensive database.

The key findings, as stated in the presentation, while the modality of locoregional therapy did not appear to be important in determining outcome, the use of increasing number of locoregional therapy treatments was associated with a higher risk of recurrence. A pathological complete tumor response and a reduction in AFP after treatment were both associated with reduced recurrence and better survival. Interestingly, the patients who had locoregional therapy and did not achieve pathological complete response had a higher risk of recurrence than patients who did not receive any at all.

I have several comments and questions. First, while the primary objective was to examine the impact of therapy on post–transplant survival, this data set does not include dropouts from the wait list. The locoregional therapy issue really needs to be considered in the context of preventing dropout because we, as transplant surgeons, principally do LRT to prevent dropout and less so to prevent recurrence after transplant.

Second, the study could definitely be strengthened with the addition of an analysis of waiting time for transplant. If waiting time proved to be a significant predictor of outcome, it could be used as a potential justification for increased use of living donor transplantation. I was wondering, was waiting time not available for all the participating centers?

The study looks at explant pathology and tumor viability, but does not include data on radiologic response to each treatment before transplant. In other words, were there indications for initial treatment and then for the repeat treatments? One would assume that the increasing number of locoregional therapy treatments was related either to waiting time or to tumor aggressiveness. Is it one or the other, or is it both? It seems that the key parameter is whether or how difficult it is to achieve satisfactory radiological tumor response before transplant and that the number of treatments are likely a surrogate marker for this.

The more locoregional therapy treatments correlated with worse outcome, but did the outcome differ by number of locoregional therapy treatments in the subgroup who did achieve complete pathological response?

Do you know why the locoregional therapy was not used in some patients, and was this due to severity of disease, or was it due to just the short waiting times within that region or at that center?

And from a policy perspective, I think it would be very difficult to integrate the number of treatments in patient selection or allocation for transplant as this could be highly variable depending on clinical practice or regional variations, and not to mention it might lead to wrongly withholding locoregional therapy when it is clinically needed. In addition, I think this provides one more difficulty in modeling any response for new rules based on retrospective data for future allocation.

I think in the future, the paper could benefit from examining center and region effect as it obviously may include a variation in practice pattern, donor availability, and OPO performance, and further grouping centers by ''high MELD'' at transplant or ''lower MELD at transplant'' may elucidate a variation in practice depending on perceived time to transplant.

My final point is not a question but just a caution; that it would be wrong to conclude from this study that the use of locoregional therapy is harmful or not helpful. While the authors do not implicitly state this conclusion, it may be implied from the results that increasing number of treatments has a negative effect, and perhaps the paper would benefit from more emphasis and the readers cautioned against this erroneous conclusion.

Thank you for the opportunity to discuss this excellent paper.

Response from Dr V.G. Agopian (Los Angeles, CA):

Thank you, Dr Olthoff, for your very thorough and insightful comments.

Regarding an intent-to-treat analysis of all listed patients including those experiencing wait list dropout, unfortunately, this consortium database has data focusing only on patients who actually underwent transplant. We absolutely agree that having the cohort receiving locoregional therapy, but experiencing drop out is important, and we plan to gather data for this cohort as well. But, as you know, there are a lot of studies that have already proven that locoregional treatment is important to prevent wait list dropout. Given the increasing waiting times with the new UNOS allocation policies, our main objective in this study was to really evaluate in a large cohort what the impact of locoregional therapy was on post-transplant outcomes.

Regarding evaluation of wait times, you are correct—that information would be very helpful to have had, but currently we do not have that datapoint for all centers. One of the challenges in putting together a big consortium database is to not overburden collaborators with an excessive number of datapoints that you ask for. The wait time for transplant has clearly proven to be an extremely important factor; so now we have gone back and actually asked all the centers to provide the individual wait times for each of the patients so we can do that analysis. However, as a surrogate analysis, we did look at UNOS regions that traditionally have short wait times, regions 3 and 10, and compared them to the long wait-time regions—1, 5 and 9, and found that the short wait-time regions were much more likely to have fewer treatments, either 0 or 1 treatment, and long wait-time regions were much more likely to have 2, 3, and occasionally 4 or more treatments. Important studies have shown that rushing a patient too quickly to transplant in the short wait-time regions may negatively impact the post-transplant outcomes because you haven't had time to observe the tumor biology. So, in this sense, we're finding that an increasing number of treatments, which is seen in the long wait-time regions, is independently predicting poor outcomes, despite the fact that the short wait-time regions have traditionally done worse. Since this is the opposite effect of what we would have expected, we can say with some certainty that the number of treatments is a good surrogate for tumor biology, and appears to be independent of the effect of wait times.

In terms of radiologic response to treatment, I think this is a critical analysis to have, but also very difficult to obtain in a retrospective fashion. Even in our own single-center experience, it's challenging and time-intensive to re-review all these radiographic studies; so, for that reason, we were not able to include that assessment in the consortium database. So, I think your comment is correct, and we have to assume that what is happening is that the need for an increasing number of treatments is really in response to interval imaging studies that show either a persistent, progressive, or de novo lesion that's being targeted.

Regarding why some patients did not receive locoregional therapy, I think both of your proposals are correct. Some of it is the wait-time regions. If you anticipate in region 3 you're going to get a transplant in three months, there's no reason to treat that patient, perhaps. But we also show in our slides comparing recipient characteristics that patients not receiving locoregional therapy had statistically significantly greater MELD scores, and also radiographically smaller tumors. So, I do think that recipients with smaller tumors, and more advanced liver disease were less likely to get locoregional therapy.

Regarding the difficulty in incorporating our findings into policy, I agree with you completely, and that is probably one of the most important challenges we face. I think the easy job that we had was to try to use this big database to identify factors that are reflective of underlying tumor biology. The much harder question is, where do we draw the line? What's a recurrence risk that's unacceptable? And certainly, in terms of your last comment, we certainly don't want to imply that patients shouldn't be treated because they are getting penalized. If you need treatment to prevent wait–list dropout, we certainly don't want to discourage that. However, as a transplant community, we also have to recognize that somebody who has received seven TACE treatments is probably going to have much higher risk of developing post–transplant recurrence, and perhaps is not an ideal candidate for liver transplantation. So, these factors need to be incorporated into an allocation policy, but how they will be incorporated, I think, is a very tough question.

Thank you very much for your comments.

Dr P.-A. Clavien (Zurich, Switzerland):

Congratulations for this important large multicentric study targeting a complex and heterogeneous population of patient with HCC. Outcome in such population is influenced by many factors other than the tumor characteristics, including many recipient-dependent factors. Since many colleagues are lining up for questions, I will limit my intervention to 2 questions.

First, we hold a consensus conference on HCC a few years ago in Zurich, also covering the same topic (Lancet Oncology 2012, 13:11–21). One of the statements was that if tumors are less than 3 cm and the predicted waiting time less than 6 months, there is no evidence for a benefit for bridging locoregional therapy. Does your data support this statement?

Next, some investigators have suggested, although never really demonstrated, the TACE may increase the risk of developing extrahepatic metastases post-transplant. So, in such a large cohort, were you able to test this claim. Did you observe more tumors outside of the liver in TACE patients?

Thank you very much.

Response from Dr V.G. Agopian (Los Angeles, CA):

Thank you very much, Dr Clavien, for your comments. In terms of the consensus conference recommendations, I think we see those recommendations reflected in our data. In our multicenter cohort, 20% of patients did not receive treatment, and this was more likely for patients in UNOS regions where the anticipated wait times were less than 6 months. Furthermore, we also found that patients with smaller tumors were less likely to receive treatment.

So, one of the primary reasons for this current study was to really evaluate in a large cohort the impact on post-transplant outcomes of the actual locoregional therapy. This was especially important to study now, because we all feel that soon in the United States with the mandatory 6-month waitlist before receiving MELD exception points, we're no longer going to have any patients that are not going to be receiving treatment anymore. So, this was the ideal time to really examine the difference between patients that received treatment and did not receive treatment to try to iron out some of these issues.

Regarding TACE and extrahepatic metastases, this current analysis only looked at whether the patient recurred or not. We do have data and granularity about where they recurred and how they recurred, and that's something that we certainly will need to analyze. I agree completely.

Dr R. Fisher (Boston, MA):

I also rise to congratulate you on this presentation, this work, but more importantly how clearly and concisely you presented such a complex study.

My 2 questions are actually, 1, in this review of recurrence and in your explant pathology, I think you need to actually focus in on how many synchronous tumors that were not appreciated by your MR studies or whatever technology you used in these different centers that were related to the stage of the explant pathology when the transplant was done. I think, secondly, in your conclusions, to say that bridging with these type of multimodality therapies for HCC does not improve post-transplant survival is probably not true, because if you looked at it from an intent to transplant, more patients are being transplanted, and yet your recurrence-free survival was still 10%, quite excellent, even in this day of cancer transplantation.

So, in the end, I think that the statement should be that if we increased the number of cancers, and especially if we look beyond this to downstaging T-3-type tumors, then I think we have to relook at

this and not put a negative spin, as Kim was saying, on the use of pretransplant HCC ablation. Thank you.

Response from Dr V.G. Agopian (Los Angeles, CA):

Thank you, Dr Fisher. I agree 100%, and we certainly don't want to send that message that locoregional therapy is harmful. I think our data simply highlight that the need for increasing treatments is more of a marker of aggressive tumor biology. The hard part is knowing if you have a complete pathologic response. In patients who ultimately prove to have a complete pathologic response on explant, there's no question that receiving locoregional treatment helped. However, for patients not achieving a complete response, we're basically making the observation that it didn't seem to have a benefit in terms of reducing post-transplant recurrence.

Regarding looking at explant pathology, we do have a lot of granularity in the data about how many tumors were present on the explant. However, our radiologic assessments were simplified to categorizing patients by radiological Milan criteria and the maximum tumor diameter, so it will be difficult to iron out in this dataset how often occult multifocal disease is observed. Other studies however have clearly shown that the explant pathology always upgrades or upstages the patient 20% to 30% of the time.

Dr J. Emond (New York, NY):

I would like to echo the intent-to-treat concept. Did you actually gather data on the entire cohort of subjects that were listed at those centers? Because that's really the next thing to do.

Response from Dr V.G. Agopian (Los Angeles, CA):

Dr Emond, I think that's right. As mentioned, we don't have that intent-to-treat data in this consortium database, but as some of the single centers do, and we definitely will attempt to build that cohort for analysis.

Dr J. Emond (New York, NY):

I think if we were at a pancreatectomy cancer meeting and we were complaining about a 70%, 5-year survival, we would be in a whole different place, wouldn't we?

Response from Dr V.G. Agopian (Los Angeles, CA):

Yes. Thank you, Dr Emond.

Dr A.G. Tzakis:

I enjoyed the paper, and it clarified a lot of areas in our work. Did you consider the use of radioactive beads, whether they made a difference in the outcome?

Response from Dr V.G. Agopian (Los Angeles, CA):

Thank you, Dr Tzakis. In the approximately 5% of patients who received ''other modalities,'' I would say the majority of them are radioembolization. For patients within Milan criteria who have smaller tumors, there's just not too many centers going directly to the use of Y-90; however, some centers exclusively use radioembolization. In this consortium database, the number of patients receiving radioembolization were pretty small, so it's a little bit hard to tease out any differences. However, we didn't observe any differences on outcomes in the subset treated with Y-90.