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ORIGINAL ARTICLE

Repeated loco-regional therapies for hepatocellular carcinoma is associated with inferior outcome after living donor liver transplantation in cirrhotic patients

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Abstract

Background: Liver transplantation is the definitive treatment for defined stage hepatocellular carcinoma (HCC) in cirrhotic patients. Loco-regional therapy (LRT) may be considered before transplantation to prevent the disease progression and the patient from dropping out of the waiting list. This study aims to evaluate the impact of repeated pretransplant LRTs on the long-term outcomes in HCC liver transplant recipients.

Methods: Between 2004 and 2019, living donor liver transplantation (LDLT) recipients with viable HCC on the explant livers were enrolled. Uni- and multivariate analysis was performed with the Cox regression model to stratify the risk factors associated with HCC recurrence and patent survival after LDLT.

Results: A total of 124 patients were enrolled, in which 65.3% (n = 81) were Barcelona Clinic Liver Cancer classification stage B or D and 89% (n = 110) had advanced fibrosis or cirrhosis on the explanted livers. After a median follow-up of 41 months (IQR: 24–86.5), there were 18 cases (13.7%) of HCC recurrence. Univariate analysis showed that the model of end-stage liver disease and Child-Turcotte-Pugh score, pretransplant alpha-fetoprotein value (>500 ng/ml), repeated pretransplant LRTs (N > 4), increased tumor numbers and maximal size, presence of microvascular invasion, and the histological grading of the tumors are risk factors of inferior outcomes. In multivariate analysis, only repeated pretransplant LRTs (N > 4) had a significant impact on both the overall- and recurrence-free survival. The impact of pretransplant LRT was consistently significant among subgroups based on their LRT episodes (N = 0, 1–4, >4 respectively).

Conclusion: Repeated LRT for HCC can be associated with the risk of tumor recurrence and inferior patient survival after LDLT in cirrhotic patients. Early referral of those eligible for transplantation may improve the treatment outcomes in these patients.

Keywords: Hepatocellular carcinoma; Liver transplantation; Living donor liver transplantation; Loco-regional therapy; Outcomes

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death worldwide,[1] with over 780 000 deaths in 2018.[2] Without adequate treatment, it has a 5-year survival of 18%, which makes it the second most lethal tumor after pancreatic cancer.[3] The treatment options include radiofrequency ablation (RFA) and surgical resection for early-stage tumors with preserved liver function, and trans-arterial chemoembolization (TACE) chemoembolization for patients with multiple HCCs.[4] Liver transplantation (LT), on the other hand, provides long-term survival for cirrhotic patients with HCC under defined criteria.[5,6]

In addition to the curative intent, loco-regional therapies (LRTs, including trans-arterial chemoembolization and thermoablation) could be used to serve as the "down-stage" modality to bridge the patients to the transplantation.[7] Once the tumor is successfully down-staged, early liver transplantation provides survival benefits compared to those without transplantation.[8] Nonetheless, due to organ shortages and the uncertainties of surgical risk, patients in Taiwan with nonresectable HCCs would stay on LRTs as the main treatment option. Liver transplantation, in this context, is generally offered as the "salvage treatment" for those with persistent viable tumors after repeated LRTs. This study aims to evaluate the impact of repeated pretransplant LRTs on the long-term outcomes in HCC liver transplant recipients.

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2. METHODS

2.1. Study population and data collection

Adult patients who underwent living donor liver transplantation (LDLT) at Taipei Veterans General Hospital in Taiwan, between December 2004 and September 2019, were retrospectively reviewed. Patients with histological evidence of viable HCC on the explant liver were enrolled for outcome analysis. In our institute, the treatment options for HCC are based on the recommendations from the Barcelona clinic liver cancer (BCLC) guidelines and made by multidisciplinary medical specialists. For those considered for transplantation, we adopted the expanded set of criteria proposed by the University of California San Francisco (UCSF criteria) for patient selection for LDLT. The serum tumor marker, alpha-fetoprotein (AFP) was routinely tested during the pretransplant survey, but the level of the tumor marker alone did not preclude the patient from LDLT if the tumor burden was within the UCSF criteria.

2.2. Liver transplantation and follow-up

All patients underwent standard partial graft liver transplantation from their living related donors. The immunosuppressant regimen consisted of intraoperative induction of methylprednisolone 1 g and then tapered to oral prednisolone 20 mg on the 7th postoperative day. Steroids were generally withdrawn at 3 months after transplantation. The main maintenance immunosuppressant was Tacrolimus (Astellas Pharma, Osaka, Japan). The dosage of Tacrolimus was 0.025–0.15 mg/kg/day in two divided doses. The trough blood level was kept between 5 ng/mL and 7 ng/mL.

In addition to the regular blood tests for liver biochemistries, the post-transplant follow-up for these HCC patients included image studies (liver ultrasonography or CT scans) and tumor marker (AFP) tests at 3–6-month intervals during the first year and annually afterward.

The clinical variables, including age, gender, background liver disease, model of end-stage liver disease (MELD) and Child-Pugh score, serum AFP, the courses of LRTs before transplantation, the tumor status (within/outside Milan/UCSF criteria, BCLC stage, with/without microvascular invasion, and histology grade), and the degree of fibrosis on the explant livers were recorded. The patients were divided into two groups: those who underwent liver transplantation without pretransplant LRT (primary LDLT group), and those who received LRT before transplantation (salvage LDLT group). The clinical variables, overall survival (OS), and recurrence-free survival (RFS) were compared between these two groups using the Student's *t*-test for continuous variables, the Chi-square test for categorical variables, and the Kaplan–Meier method for survival analysis. In addition, uni- and multivariate analyses with the Cox regression model were carried out to stratify the risk factors associated with HCC recurrence after LDLT. All statistical analyses were performed using the SPSS statistical software package version 25.0 (SPSS, Inc., Chicago, IL, United States) for Windows. *p* values less than 0.05 were considered statistically significant.

3. RESULTS

Between December 2004 and September 2019, a total of 401 patients underwent LDLT at our institute. Among them, 156 patients were transplanted with indications of HCC. To specifically evaluate the cancer-related long-term outcomes, patients without viable HCC (n = 19), patients with tumors other than HCC (n = 2, cholangiocarcinoma) on the explant liver, and patients with surgical mortality (n = 11) were excluded. As a result, 124 patients were enrolled for outcome analysis (Fig. 1). Their

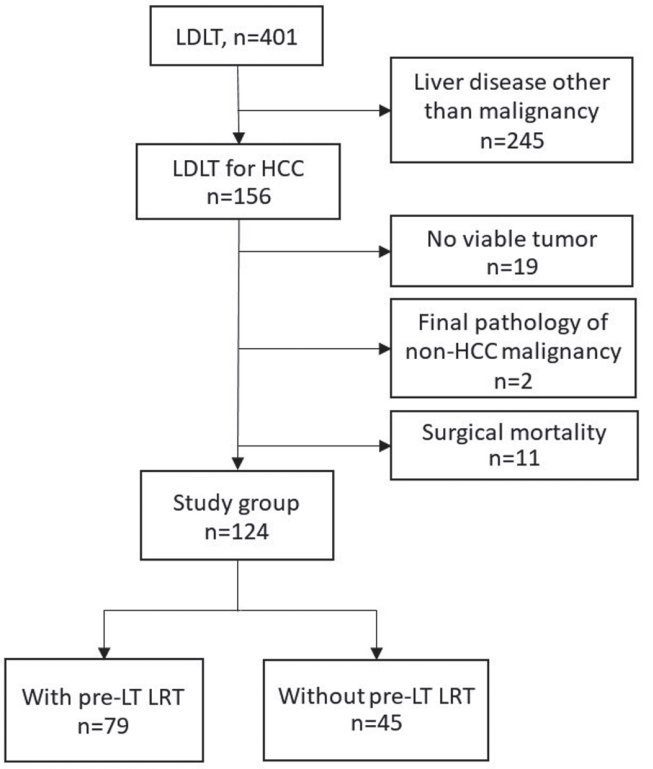

Fig. 1 A total of 401 patients underwent LDLT at our institute. 156 patients were transplanted with the indication of HCC. Patients without viable HCC (n = 19), with tumors other than HCC (n = 2, cholangiocarcinoma) on the explant liver, and patients with surgical mortality (n = 11) were excluded. As a result, 124 patients were enrolled for outcome analysis. HCC = hepatocellular carcinoma. LDLT = living donor liver transplantation.

demographic data are listed in Table 1. Among these patients, 89% (n = 110) had advanced fibrosis (Ishak grade 5; n = 5) or cirrhosis (Ishak stage 6; n = 105) on the explanted livers. For those without evidence of advanced fibrosis on explant livers, most of them had evidence of advanced portal hypertension (e.g., prominent esophageal/gastro-varices, the presence of splenomegaly or portal-systemic shunt, recanalization of the umbilical vein, massive ascites, etc.). Regarding to their oncological status, more than half (65.3%) of the patients were classified as BCLC intermediate stage (n = 37, 29.8%) or terminal stage (n = 44, 35.5%). Ninety-five patients (76.6%) had moderately/poorly tumor differentiation, and 73 patients (58.9) had microvascular tumor invasion on histological examination of the explanted livers.

Among the study group, 45 patients received LDLT without pretransplant LRT (primary LDLT group) and 79 patients received LRTs before LDLT (salvage LRT group). To compare with the salvage LDLT group, patients in the primary LDLT group had more advanced liver disease (as shown by the higher percentage of Child B/C and higher MELD score) before transplantation. The baseline AFP level has no difference between these two groups, but the tumor burden (number/size and histologic grading) was more advanced in the salvage LDLT group with more patients who had tumors exceeding the Milan/UCSF criteria on explant livers (Table 2).

Among the 79 patients in the salvage LT group, the pretransplant LRT consisted of TACE alone in 29 patients (36.7%), thermal ablation alone in 11 patients (13.9%), resection alone in 1 patient (1.27%), and combined treatment modalities in the rest half (n = 39, 49.3%). Fifty-four patients (68.4%) had repeated LRTs, whereas 25 patients (31.6%) had more than four episodes

Table 1

Demographic profile of study patients (n = 124)

Median follow-up time (month)	[a]41 (24–86.5)
Loss of follow-up	3 (2.4%)
Gender (male/female)	88 (71.0%)/36 (29.0%)
Age	[a]58 (28–75)
CTP score	A: 35 (28.2%), B: 45 (36.3%), C: 44 (35.5%); median: 9
MELD score (Median)	[a]14 (10–20)
Within Milan Criteria	74 (59.7%)
Within UCSF Criteria	85 (68.5%)
Underlying liver disease	
HBV	67 (54.0%)
HCV	31 (25.0%)
HBV + HCV	4 (3.2%)
Alcoholic	19 (15.3%)
Recurrence No.	18 (13.7%)
BCLC stage	
Very early stage (0)	2 (1.6%)
Early stage (A)	41 (33.1%)
Intermediate stage (B)	37 (29.8%)
Advanced stage (C)	0 (0%)
Terminal stage (D)	44 (35.5%)
Microvascular invasion (mVI)	
With mVI	50 (40.3%)
Without mVI	74 (59.7%)
Histology grade	
Well differentiated	26 (21.0%)
Moderately diff.	78 (62.9%)
Poor diff. or undiff.	17 (13.7%)
Ishak fibrosis stage	Gr. 6: 105 (85%), Gr. 5: 5 (4%), Gr. 2-4: 11 (9%), omitted: 3 (2%)

BCLC stage = Barcelona Clinic Liver Cancer stage; CTP = Child-Turcotte-Pugh score; diff.=differentiated. Histology grades were not recorded in 3 case (2.4%); HBV = hepatitis B virus; HCV = hepatitis C virus; IQR = interquartile range; MELD = model for end-stage liver disease.
[a]Median (IQR).

of LRTs before LDLT. The treatment modalities and episodes were summarized in Table 3.

After a median follow-up of 41 (IQR: 24–86.5) months, there were 32 cases (25.8%) of patient death and 18 cases (13.7%) of HCC recurrence. The OS rates at 1-, 3-, and 5-year post-LDLT were 92.7%, 81.9%, and 70.8% respectively (BCLC stage A/B/D: 81.7%, 54.0%, 76.2% respectively); the RFS rates were 94.1%, 82.9%, and 81.4% respectively (BCLC stage A/B/D:81.6%, 68.9%, 92.1% respectively). Direct comparison between the two groups showed that salvage LDLT was associated with inferior outcomes compared to primary LDLT (5-year OS 61.7% vs 87.5%, $p = 0.012$, 5-year RFS 70.7% vs 100.0%, $p = 0.001$) (Fig. 2).

To further define the possible risk factors that may impact the long-term outcomes, the demographic and pathological factors were adopted in the regression model for uni-/multi-variant analysis. On uni-variant analysis, several factors including The Child-Turcotte-Pugh score (CTP score), the MELD score, pretransplant AFP value (cut-off set at 500 ng/ml), LRT numbers, and tumor status (within/outside Milan or UCSF criteria, tumor number, and maximal size) and the histological grading were associated with significant negative impacts on post-transplant OS/RFS (Tables 4and 5). On multi-variant analysis, although certain factors (such as the MELD score or the tumor size/histological grading) remained significant on OS or RFS, only repeated pretransplant LRTs (>4 times) was an independent factor for both OS and RFS (OS: CI, 1.369–5.539, $p = 0.004$; RFS: CI, 1.448–22.80, $p = 0.013$) (Tables 4 and 5). Subgroup analysis demonstrated that both the OS and RFS were gradually improved in parallel with the decrease of pretransplant LRT episodes (N = 0, 1–4, >4, respectively) (Fig. 3). (Patient demographics and tumor histological findings between LRT1–4, LRT>4 subgroups were compared and listed in Table 6).

Table 2

Comparison of demographic among hepatocellular carcinoma patients underwent primary or salvage liver transplantation

	Primary LT (n = 45)	Salvage LT (n = 79)	*p*
Age	57.42 + 8.2	57.15 + 7.7	0.79
Male gender	30 (58%)	58 (66%)	0.40
Background liver disease			
HBV	25 (57%)	42 (55%)	0.86
HCV	9 (20%)	22 (29%)	0.29
HBV+HCV	3 (6.7%)	1 (1.3%)	0.10
Alcoholic	7 (8.9)	12 (15.2)	0.96
CTP gr. A/B/C	7%/33%/60%	41%/38%/21%	< 0.001
MELD score (median)	17 (14–23)	12 (10–18)	0.001
Pre-LT AFP	8.82 (4.63–42.27)	9.53 (3.68–39.1)	0.270
Within Milan	35 (77.8%)	39 (49.4%)	0.002
Within UCSF	40 (88.9%)	45 (57.0%)	< 0.001
BCLC stage 0/A/B/D	2.2%/31.1%/6.7%/60.0%	1.3%/35.1%/41.6%/22.1%	< 0.001
Tumor no (median)	1 (1–5)	3 (1–numerous)	0.018
Max. tumor size (median)	2.7 (0.3–4.5)	2.4 (0.5–9.5)	0.41
Histology grade			0.038
Well differentiated	15 (33.3%)	11 (14.5%)	
Moderately diff.	26 (57.8%)	52 (68.4%)	
Poor diff. or undiff.	4 (8.9%)	13 (17.1%)	

The data are presented as medians and interquartile ranges.
AFP = alpha-fetoprotein; BCLC stage = Barcelona Clinic Liver Cancer stage; CTP = Child-Turcotte-Pugh score; diff.=differentiated. Histology grades were not recorded in 3 case (2.4%); HBV = hepatitis B virus; HCV = hepatitis C virus; IQR = interquartile range; LT = liver transplantation; MELD = Model for End-Stage Liver Disease.

4. DISCUSSION

The value of liver transplantation in the treatment of HCC was considered controversial until 1996 when Mazzaferro et al published the promising results of liver transplantation for

Table 3

Distribution of pretransplant locoregional treatment modality and number

LRT modality	N	%
TACE only	28	36.7
RFA only	11	13.9
Surgical resection only	1	1.27
TACE and RFA	17	21.5
Miscellaneous	22	27.8
Number of treatments		
1	25	31.6
2	15	19.0
3	6	7.6
4	8	10.1
≥5	25	31.6

"Miscellaneous" includes combined treatments of TACE, RFA, PEI (percutaneous *ethanol* injection), and/or surgical resection.
LRT = loco-regional therapy; RFA = radiofrequency ablation; TACE = Trans-arterial chemoembolization.

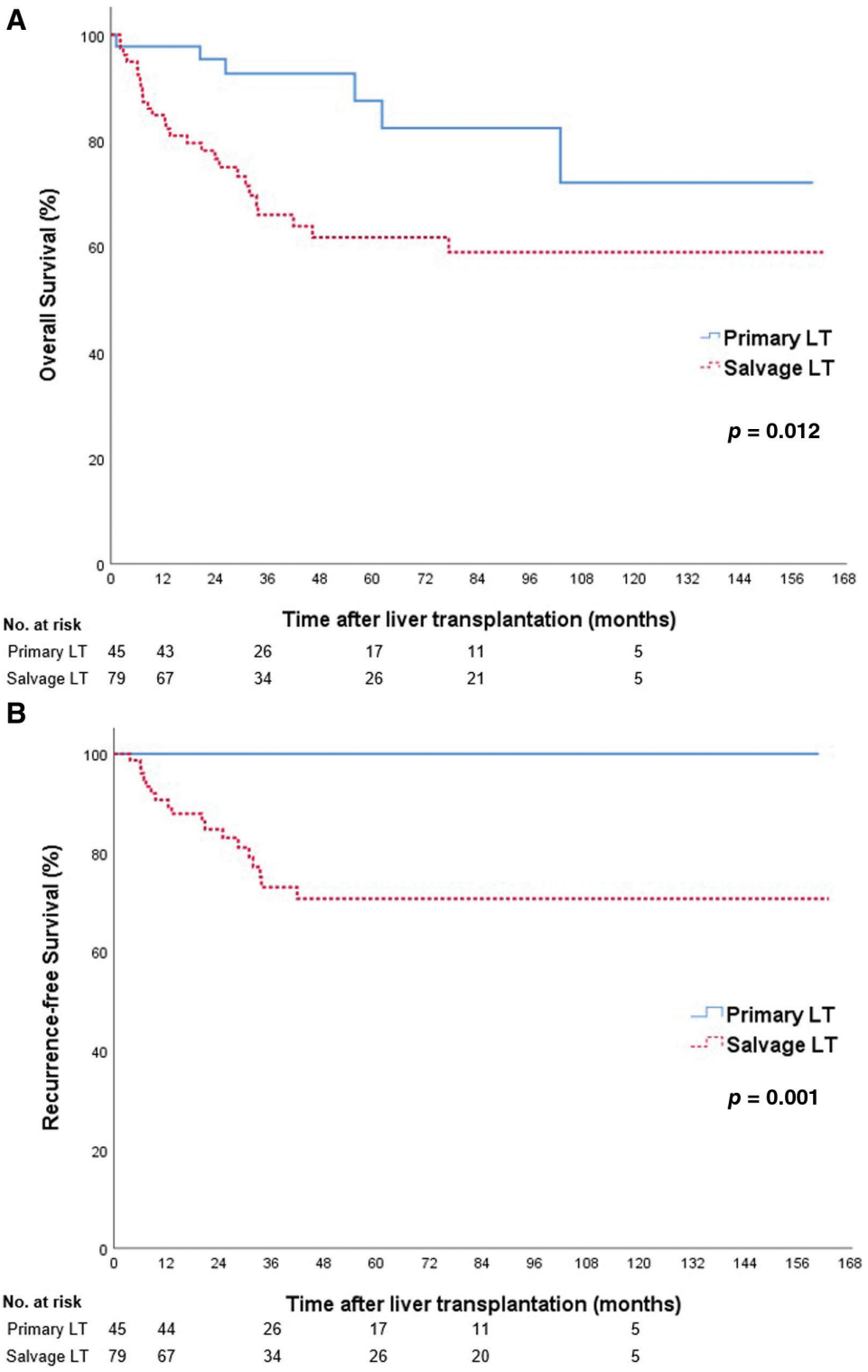

Fig. 2 Comparison between the two groups showed that salvage LDLT was associated with inferior outcomes compared to primary LDLT (5-years OS 61.7% vs 87.5%, 5-years RFS 70.7% vs 100.0%, $p = 0.001$). LDLT = living donor liver transplantation; RFS = recurrence-free survival.

small but nonresectable HCC patients. In this prospectively designed study, patients with a single tumor smaller than 5 cm, or patients with multiple tumors numbering fewer than three and each smaller than 3 cm, without evidence of vascular invasion or distant metastasis, were eligible for transplantation. The actual survival rate and RFS rate were 75% and 83%, respectively.[5] Based on this fundamental finding, several studies were designed aiming to expand the patient selection criteria while not interfering with the long-term outcomes.[6,9] For patients whose tumors were outside these criteria, liver transplantation could be performed after successful downstaging the tumor burdens by LRTs.[7,10] In a study based on a retrospective

Table 4

Multivariate analysis -for overall survival

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**CI (95%)**	***p***	**HR**	**CI (95%)**	***p***
CTP score	1.082	0.924–1.266	0.329		–	
MELD score (median)	1.046	1.011–1.081	**0.009**	1.095	1.031–1.163	**0.003**
Pre-LT AFP > 500ng/ml	4.546	1.361–15.18	**0.014**	4.352	0.974–19.448	0.054
Within Milan	1.682	0.848–3.339	0.137		–	
Within UCSF	1.682	0.847–3.340	0.137		–	
LRT > 4	2.042	1.272–3.278	**0.003**	2.754	1.369–5.539	**0.004**
BCLC stage	1.099	0.844–1.431	0.483		–	
Tumor No.	1.066	1.029–1.105	**< 0.001**	1.023	0.970–1.079	0.395
Max. tumor size	1.226	1.030–1.459	**0.022**	1.193	0.935–1.521	0.156
Histological grade	1.693	0.941–3.044	0.079		–	
Microvascular invasion	1.612	0.853–3.047	0.142		–	

AFP = alpha-fetoprotein; BCLC stage = Barcelona Clinic Liver Cancer stage; CI = confidence interval; CTP = Child-Turcotte-Pugh score; HR = hazard ratio; LT = liver transplantation; LRT = Loco-regional therapy; MELD = Model for End-Stage Liver Disease.

review of the United Network for Organ Sharing database, the overall survival in the down-staged patients is comparable with those that initially met the Milan criteria.[7] Nonetheless, the clinical benefits may be limited to those with good responses to the pretransplant downstaging, especially those with extensive tumor necrosis after LRT.[11,12] For those whose tumors do not properly respond to the treatment, repeated LRTs may also cause a detrimental effect on the post-transplant outcomes.

Based on the analysis from a US multi-center database consisting of more than 3000 cases, Agopian VG et al disclosed that patients receiving pre-transplant LRTs more than four times are associated with inferior post-transplant outcomes in terms of higher recurrence rates.[11] It is arguable that the negative impact of repeated LRT may be a reflection of the biological behavior of the tumor itself since only those with persistent viable tumors need repeated LRT. To avoid this possible confounding factor, we excluded the patients whose tumors were extended necrotic after LRTs and enrolled only patients with viable tumors for analysis. In accordance with the previous data, the results from our study also disclosed that repeated LRT is an independent poor prognosis factor for both patient survival and oncological outcomes.

TACE is widely adopted as an LRT for patients with HCCs at intermediate stages.[13,14] In our study, 83.4% of the patients in the salvage transplantation group had TACE before transplantation. One of the cardinal effects of TACE is to induce hypoxic necrosis of the tumor.[15] However, the tumor may undergo a phenotype switch and display more aggressive tumor behavior under hypoxic circumstances. Using an immunohistochemistry stain and reverse-transcription polymerase chain reaction (RT-PCR) on the explant livers, Zen et al demonstrated that the expression of several progenitor markers (CD133, CD19, and EpCAM) was more prominent on the tumors of patients receiving TACE than those without TACE. Furthermore, the expression of CD 133+ tumors was associated with higher recurrence rates after transplantation.[16] In a rat hepatoma model, Ueshima et al also demonstrated that embolization of the hepatic artery would induce hypoxic stress and enhance the TGF-β/HIF-1αexpression, which results in tumor progression.[17] The presence of these hypoxic and progenitor markers on human HCCs was associated with resistance to TACE and poor clinical outcomes.[18,19] Evidence from these literatures may support our clinical findings and reveal a field that can be further investigated.

The ideal therapeutic outcome is that patients have a complete response after LRT. Nonetheless, TACE may achieve partial responses in 15%–55% of patients, with a complete response rate of less than 10%.[14,20] Even if a complete response is achieved, >40% of patients develop recurrence at 1 year after TACE with unfavorable outcomes.[21] In a prospectively designed randomized trial from the Italian group, Mazzaferro et al demonstrated a definite survival benefit of LT over repeated LRTs.[8] In their study, patients whose tumor was initially beyond the

Table 5

Multivariate analysis—recurrence-free survival

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**CI (95%)**	***p***	**HR**	**CI (95%)**	***p***
CTP score	0.748	0.953–0.943	**0.014**	0.951	0.583–1.549	0.839
MELD score (median)	0.907	0.829–0.991	**0.031**	1.061	0.925–1.217	0.398
Pre-LT AFP > 500ng/ml	5.199	1.180–22.90	**0.029**	0.793	0.123–5.116	0.807
Within Milan	3.239	1.215–8.634	**0.019**	1.489	0.124–17.927	0.754
Within UCSF	3.910	1.514–10.10	**0.005**	1.380	0.125–15.258	0.793
LRT >4	2.567	1.015–6.488	**0.046**	5.745	1.448–22.800	**0.013**
BCLC stage	0.841	0.577–1.225	0.367		–	
Tumor No.	1.073	1.020–1.128	**0.005**	0.973	0.891–1.062	0.539
Max. tumor size	1.575	1.304–1.904	**< 0.001**	1.656	1.198–2.289	**0.002**
Histological grade	3.566	1.556–8.175	**0.003**	5.276	1.460–19.067	**0.011**
Microvascular invasion	4.597	2.033–10.395	**< 0.001**	5.315	0.938–30.133	0.059

AFP = alpha-fetoprotein; BCLC stage = Barcelona Clinic Liver Cancer stage; CI = confidence interval; CTP = Child-Turcotte-Pugh score; HR = hazard ratio; LT = liver transplantation; LRT = loco-regional therapy; MELD = model for end-stage liver disease.

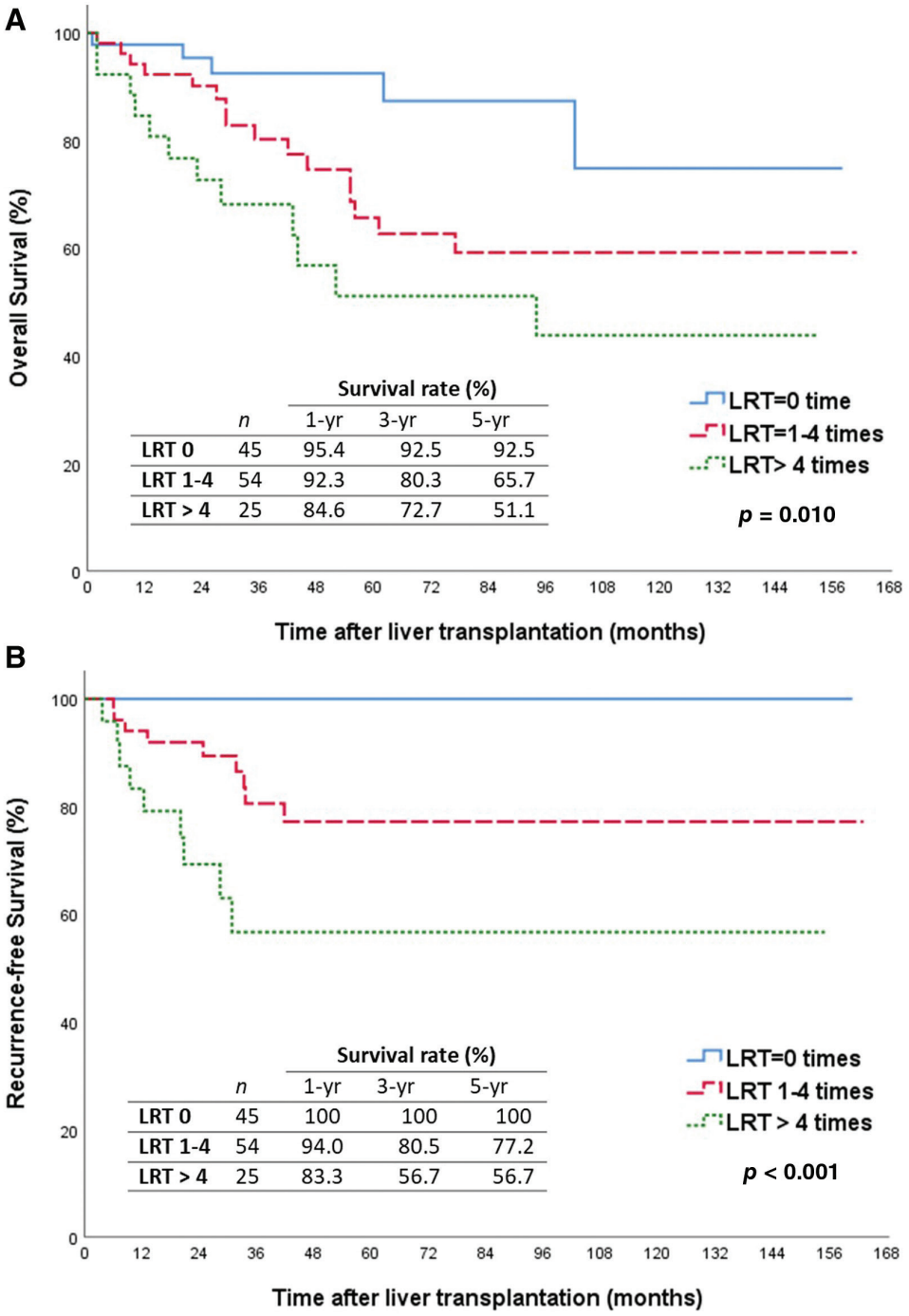

Fig. 3 Subgroup analysis showed patients that received pre-transplant LRTs more than four times were associated with the worst outcomes, followed by patients that received LRTs 1–4 times (OS/RFS $p = 0.01$ / $p < 0.001$). LRT = Loco-regional therapy; OS = overall survival; RFS, recurrence-free survival.

Milan criteria were recruited and treated by LRT first. Once the tumors were successfully down-staged, these patients were randomly assigned to the transplantation vs. control (keep on LRT) groups. The results showed 77.5%/76.8% 5-year OS/RFS rate in the transplantation group vs. 31.2%/18.3% in the control (nontransplant) group ($p < 0.05$).[8] Taken together, these results suggest that LRT should be the therapeutic option for patients whose tumor initially is beyond the transplant criteria, but liver transplantation should be considered earlier once the tumor has been successfully down-staged.

There are certain limitations in this retrospective study. First, the heterogeneities on patient demographics and tumor histology among study groups could not be completely avoided; since more patients in the primary LT group might be transplanted for their advanced liver disease (higher proportion of CTP B/C and higher MELD score) rather than the oncological considerations, and more patients in the salvage LT group might be treated by LRTs because of the advanced tumor burdens with tolerable liver functions (Table 2 and 6). Based on this, we adopted all these demographic and histological factors for multi-variant

Table 6

Comparison of demographic among different number of loco-regional therapy

	LRT1–4 (n = 54)	LRT >4 (n = 25)	*p*
Age	57.27 ± 7.57	56.76 ± 8.42	0.789
Male gender	35 (64.8%)	22 (88.0%)	**0.047**
Background liver disease			
HBV	28 (51.9%)	16 (64.0%)	0.450
HCV	16 (29.6%)	4 (16%)	0.210
HBV+HCV	0 (0%)	1 (4%)	0.150
Alcoholic	9 (16.7%)	2 (8%)	0.261
CTP gr. A/B/C	39%/41%/20%	56%/24%/20%	0.183
MELD score (median)	15 (9–17)	14 (10–18)	0.515
Pre-LT AFP	8.79 (3.65–39.15)	15.65 (5.05–78.43)	0.852
Within Milan	32 (59.3%)	9 (36.0%)	0.087
Within UCSF	37 (68.5%)	10 (40%)	**0.027**
BCLC stage 0/A/B/D	1.9%/50.0%/27.8% /20.4%	0%/16%/64% /20%	**0.020**
Tumor no (median)	2 (1–3)	8 (1–numerous)	**<0.001**
Max. tumor size (median)	2.75 (1.85–4.00)	2.8 (2.30–4.15)	0.617
Histology grade			0.667
Well differentiated	6 (12.0%)	4 (16.0%)	
Moderately diff.	37 (74.0%)	16 (64.0%)	
Poor diff. or undiff.	7 (14.0%)	5 (20.0%)	

The data are presented as medians and interquartile ranges.

AFP = alpha-fetoprotein; BCLC stage = Barcelona Clinic Liver Cancer stage; CTP = Child-Turcotte-Pugh score; diff.=differentiated. Histology grades were not recorded in 3 case (2.4%); HBV = hepatitis B virus; HCV = hepatitis C virus; LT = liver transplantation; LRT = loco-regional therapy; MELD = model for end-stage liver disease.

analysis and showed that repeated LRT was the only definite risk factor for both OS/RFS. Second, the actual number of "delay-referral" (patients who had successful down-staged of the tumor but still remained on LRT) was hard to define, but we did notice that 56 of the salvage LT patients had their tumors initially met the UCSF criteria but still underwent episodes of LRT before transplant. Based on the rationale that repeated LRT may be associated with a more aggressive tumor behavior and liver transplantation proves the survival benefit over LRT after successfully down-staging,[8] results from our study may suggest that early transplantation improves the treatment outcomes in our cohort.

In conclusion, we report a single-center, retrospective analysis of liver transplantation for HCC and demonstrated the negative impact of repeated loco-regional therapies on the post-transplant outcomes. Therefore, early referral of those eligible for transplantation may improve the treatment outcomes in these patients.

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