

## Clinical usefulness of transarterial chemoembolization response prior to liver transplantation as predictor of optimal timing for living donor liver transplantation

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**Purpose:** Response to preoperative transarterial chemoembolization (TACE) has been recommended as a biological selection criterion for liver transplantation (LT). The aim of our study was to identify optimal timing of living donor liver transplantation (LDLT) after TACE based on the TACE response.

**Methods:** We performed a retrospective study to assess recurrence in 128 hepatocellular carcinoma (HCC) patients who underwent LDLT following sequential TACE from January 2002 to March 2015 at a single institute. Cox proportional hazard models and Kaplan-Meier analysis were utilized to estimate HCC recurrence and find optimal timing for LDLT.

**Results:** Seventy-three and 61 patients were divided as the responder and nonresponder, respectively. Multivariate analysis showed independent pre-liver transplantation (pre-LT) predictors of recurrence were larger sized tumor (>3 cm,  $P = 0.024$ ), nonresponse to TACE ( $P = 0.031$ ), vascular invasion ( $P = 0.002$ ), and extrahepatic nodal involvement ( $P = 0.001$ ). In the 3-month time difference between last pre-LT TACE and LDLT subgroup, TACE responders showed significantly higher adjusted hazard ratio (aHR) of recurrence free survival (aHR, 6.284;  $P = 0.007$ ), cancer specific survival (aHR, 7.033;  $P = 0.016$ ), and overall survival (aHR, 7.055;  $P = 0.005$ ). Moreover, for overall patients and responder groups, the significant time difference between last pre-LT TACE and LDLT was 2 months in the minimum P-value approach.

**Conclusion:** In selected patients who showed good response to pre-LT TACE, a shorter time interval between TACE and LDLT may be associated with higher recurrence free survival, cancer specific survival, and overall survival.

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**Key Words:** Chemoembolization, Liver transplantation, Hepatocellular carcinoma

### INTRODUCTION

Since deceased donor liver transplantation (DDLT) for the treatment of small hepatocellular carcinoma (HCC) was first reported by Mazzaferro et al. [1] in 1996, liver transplantation (LT) has been considered the treatment option providing the best chance of a cure for unresectable HCC with liver cirrhosis.

In most Asian countries, although there have been various issues regarding optimal tumor criteria selection for LT [2-6], an extreme shortage of deceased donors and the strong clinical needs for LT in patients with combined HCC and chronic HBV has led to the establishment of living donor liver transplantation (LDLT) as a practical alternative to DDLT [7,8].

Transarterial chemoembolization (TACE) is a key bridging

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and downstaging treatment for unresectable HCC in patients considering LDLT as well as patients on the waiting list for DDLT [9-11]. Response to TACE prior to LT has been suggested as a biological selection criterion for LT or a predictor of long-term outcome after LT [12-15]. However, the clinical impact of pre-LT TACE response has not been validated yet in LDLT recipients. In addition, for patients with advanced HCC who underwent TACE, the decision or optimal timing of LDLT as a definitive treatment option have not been well established.

We identified predictors affecting recurrence of HCC after LDLT in patients undergoing TACE prior to LDLT and assessed whether pre-LT TACE poor response was the risk factor for recurrence of HCC in LDLT recipients, similar to the case of DDLT recipients. We also investigated the clinical usefulness of pre-LT TACE response in terms of determination for optimal timing of LDLT in patients who underwent TACE as a bridging and downstaging treatment for unresectable HCC.

## METHODS

### Study design and population

We retrospectively assessed the data of 527 patients who underwent LDLT for HCC at single institution during the period between January 2002 and March 2015. Three hundred sixty-five patients underwent the treatment for HCC prior to LDLT. Those patients who underwent liver resection (LR,  $n = 10$ ), radiofrequency ablation (RFA,  $n = 29$ ), and more than two modality of combined treatment such as RFA, LR, and RT ( $n = 192$ ) were excluded from this study. Finally, 134 patients who underwent TACE only before LDLT were included in this study (Fig. 1).

The following characteristics for these 134 patients were reviewed: demographic factors (age, sex, etiology, Child-Turcotte-Pugh grade, model for end-stage liver disease score,  $\alpha$ -FP at the time of transplantation, and TACE numbers), radiologic factors (within or beyond Milan criteria based on tumor size and number using computer tomography, bilobar distribution), and pathologic factors (tumor differentiation, vascular invasion,

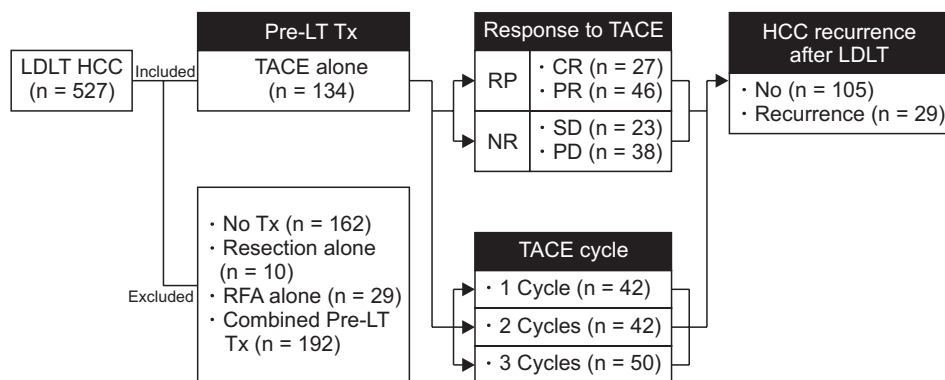
intrahepatic metastasis, portal vein thrombosis, and tumor necrosis). In addition, TACE-associated factors were reviewed: numbers of TACE cycles, time-related variables such as diagnosis-LDLT time (monthly duration from diagnosis of HCC to LDLT), first TACE-LDLT time (monthly duration from initiation of TACE to LDLT), and last TACE-LDLT time (monthly duration from termination of TACE to LDLT). This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (approval number: 2014-11-060) and informed consent was waived by the IRB.

### Statistical methods

Continuous data was represented as median with range. Categorical data was specified as numbers and percentages. Univariate and multivariate analyses for factors affecting recurrence of HCC following LDLT were conducted using a Cox proportional hazard model. In addition, Cox regression was used to calculate the adjusted hazard ratio (aHR) of recurrence free survival (RFS), cancer specific survival (CSS), and overall survival (OS) for each subgroup. The "minimum P-value" approach was used to determine the best cutoff timing for LDLT after TACE [16]. A  $P < 0.05$  was considered a statistically significant. Data handling and analyses were carried out using the IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA).

## RESULTS

Table 1 shows the demographic and clinical characteristics in the study cohort of 134 patients. Median age at transplantation was 54 years (range, 30–77 years). Male and female were comprised of 114 (85%) and 20 patients (15%), respectively. Recipients who underwent ABO incompatible LDLT were 11 patients (8.2%). The most common cause of cirrhosis was HBV (86.6%). The majority of patients (72.4%) had HCC as defined by Milan criteria. The tumors in the explant liver of 23 patients were totally necrotic and thus were unable to be assessed for tumor differentiation. In the study cohort of 134 patients undergoing TACE prior to LDLT, median clinical



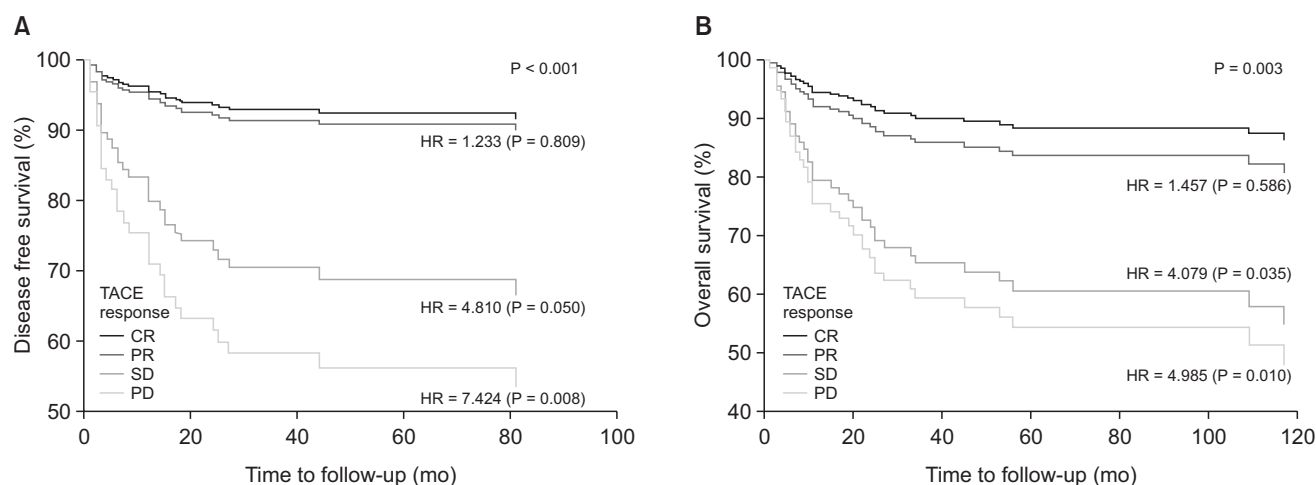
**Fig. 1.** Study design and population. LDLT, living donor liver transplantation; HCC, hepatocellular carcinoma; LT, liver transplantation; Tx, treatment; TACE, transarterial chemoembolization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RFA, radiofrequency ablation.

**Table 1.** Clinical, radiological, and pathological characteristics of 134 LDLT recipients who underwent pre-LT TACE

Characteristic	Value
<b>Clinical characteristics</b>	
Age (yr)	54 (30–77)
Male sex	114 (85.1)
Etiology	
HBV:HCV:alcohol:cryptogenic cirrhosis:unknown	116 (86.6):10 (7.5):4 (3):2 (1.5):2 (1.5)
Estimated MELD score	13.0 (-1 to 46)
Child-Pugh class (%), A:B:C	34 (25.4):50 (37.3):50 (37.3)
α-FP at LT (ng/mL)	16.2 (1.3–1133780.3)
No. of TACE	2 (1–10)
<b>Radiological characteristics</b>	
Milan criteria within	97 (72.4)
Maximum radiologic tumor size (cm)	1.8 (0.5–8.4)
≤3:>3	107 (79.9):27 (20.1)
No. of radiologic tumors	
Single:multiple	64 (47.8):70 (52.2)
Bilobar distribution	34 (25.4)
<b>Pathological characteristics</b>	
Tumor differentiation, NA:Gr1:Gr2:Gr3	23 (17.2):21 (15.7):81 (60.4):9 (6.7)
Vascular invasion	46 (34.3)
Intrahepatic metastasis	33 (24.6)
Portal vein thrombosis	32 (23.9)
Tumor necrosis (%), <50:≥50	78 (58.2):56 (41.8)

Values are presented as median (range) or number (%).

LDLT, living donor liver transplantation; LT, liver transplantation; TACE, transarterial chemoembolization; MELD, model for end-stage liver disease; NA, not applicable; Gr, grade.



**Fig. 2.** Disease-free survival (A) and overall survival (B) according to modified response evaluation criteria in solid tumors-defined transarterial chemoembolization (TACE) responses. HR, hazard ratio; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

follow-up duration after LDLT was 44 months (range, 1.0–170.0 months). Median diagnosis-LDLT time was 11.1 months (range, 1.5–122.3 months) and median first TACE-LDLT time was 10.4 months (range, 0.6–122.1 months). Median last TACE-LDLT was 5 months (range, 0.6–74.7 months). Forty-two patients (31%) underwent single TACE before LDLT. Other 42 patients

underwent 2 cycles of TACE prior to LDLT. Fifty cases of 134 patients underwent between 3 and 10 cycles of TACE before LDLT (Fig. 1).

We determined tumor response to TACE according to the last radiologic assessment before LDLT based on modified response evaluation criteria in solid tumors (mRECIST) criteria [17]. Forty-

**Table 2.** Univariate and multivariate cox analysis for HCC recurrence risk factors after LDLT

Variable	Recurrence		Univariate			Multivariate		
	No (n = 105)	Yes (n = 29)	HR	95% CI	P-value	HR	95% CI	P-value
Age (yr)	54 (30-77)	52 (37-69)	0.959	0.915-1.004	0.071			
Sex								
Male	86 (82)	28 (97)	5.080	0.691-37.340	0.110			
Female	19 (18)	1 (3)						
MELD score	14 (-1 to 46)	11 (6-23)	0.958	0.902-1.018	0.164			
Use of IL2 induction								
No	6 (6)	1 (3)						
Yes	99 (94)	28 (97)	0.763	0.104-5.616	0.790			
Serum total bilirubin before LT (mg/dL)	2.1 (0.3-50.4)	1.8 (0.4-26.4)	0.992	0.948-1.038	0.737			
Serum CRP before LT (mg/L)	0.34 (0.01-7.00)	0.86 (0.06-13.16)	1.182	1.049-1.332	0.006*	1.043	0.901-1.207	0.572
Serum $\alpha$ -FP before LT (ng/mL)								0.382
$\leq 1,000$	103 (95)	20 (69)						
$> 1,000$	2 (5)	9 (31)	9.438	4.242-21.000	$< 0.001^*$	1.678	0.526-5.355	0.090
Milan criteria								
Within	87 (83)	10 (35)						
Above	18 (17)	19 (65)	6.242	2.898-13.445	$< 0.001^*$	2.290	0.878-5.973	0.428
No. of nodules								
Single	50 (48)	9 (31)						
Multiple	55 (52)	20 (69)	2.266	1.031-4.979	0.042*	0.564	0.137-2.324	0.024*
Diameter of largest tumor								
$\leq 3$ cm	93 (89)	14 (48)						
$> 3$ cm	12 (11)	15 (52)	5.923	2.847-12.321	$< 0.001^*$	2.706	1.143-6.407	0.083
Bilobar distribution								
No	85 (81)	15 (52)						
Yes	20 (19)	14 (48)	3.249	1.565-6.747	0.002*	2.687	0.880-8.206	0.031*
TACE response								
RP	67 (64)	6 (21)						
NR	38 (36)	23 (79)	5.566	2.264-13.684	$< 0.001^*$	3.207	3.217-11.115	
TACE cycles								
Single	34 (32)	8 (28)	0.842	0.373-1.902	0.679			
Multiple	71 (68)	21 (72)						
Time between HCC diagnosis and LT (mo)	11 (1-120)	9 (1-84)	0.996	0.975-1.017	0.691			
Time between 1st TACE and LT (mo)	10 (1-122)	9 (1-83)	0.995	0.974-1.017	0.652			
Time between last TACE and LT (mo)	5 (0-11)	3 (0-10)	0.952	0.888-1.021	0.170			

**Table 2.** Continued

Variable	Recurrence		Univariate		Multivariate	
	No (n = 105)	Yes (n = 29)	HR	95% CI	HR	95% CI
Tumor grade						
NA	21 (20)	2 (7)				0.537
1	19 (18)	2 (7)	1.003	0.141–7.123		
2	60 (57)	21 (72)	3.200	0.750–13.647		
3	5 (5)	4 (14)	6.991	1.278–38.247	0.031*	0.052–4.663
Tumor necrosis						
<50	58 (55)	20 (69)				
≥50	47 (45)	9 (29)	0.519	0.235–1.142	0.103	
Vascular invasion						
No	80 (76)	8 (28)				0.002*
Yes	25 (24)	21 (72)	6.428	2.843–14.537	<0.001*	1.643–10.064
Portal vein thrombosis						
No	84 (80)	18 (62)				0.190
Yes	21 (20)	11 (38)	2.138	1.009–4.533	0.047*	0.172–1.417
Intrahepatic metastasis						
No	88 (84)	13 (45)				0.193
Yes	17 (16)	16 (55)	4.550	2.181–9.491	<0.001*	0.732–4.706
Extrahepatic nodal involvement						
No	105 (100)	28 (97)				0.001*
Yes	0 (0)	1 (3)	14.306	1.812–1112.920	0.012*	5.375–640.618

Values are presented as median (range) or number (%).

HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; HR, hazard ratio; CI, confidence interval; MELD, model for end-stage liver disease; LT, liver transplantation; TACE, transarterial chemoembolization; RP, responder; NR, nonresponder; NA, not applicable.

\*P < 0.05, significant differences.

six patients (34.3%) showed complete response (CR) to TACE and 27 patients (20.2%) had more than 30% decreases in viable tumor (PR). Twenty-three patients (17.2%) had stable disease (SD) and 38 patients (28.3%) showed progressive disease (PD) as shown at Fig. 1. The Cox proportional hazard model which evaluated tumor response to TACE showed CR patients were significantly different from SD (disease free survival [DFS],  $P = 0.050$ ; OS,  $P = 0.035$ ) and PD (DFS,  $P = 0.008$ ; OS,  $P = 0.010$ ) patients, but were not significantly different from PR (DFS;  $P = 0.809$ , OS;  $P = 0.586$ ) patients (Fig. 2A, B). In order to perform univariate and multivariate analyses regarding the effect of TACE response on recurrence of HCC after LDLT, patients were divided into 2 groups according to tumor response to TACE prior to LDLT: responders ( $n = 73$ ) and nonresponders ( $n = 61$ ). Responders included patients with CR or PR. Nonresponders included patients with SD or PD (Fig. 1).

### Univariate and multivariate analyses of factors affecting recurrence of HCC after LDLT

A univariate Cox proportional hazard model showed statistically significant risk factors for HCC recurrence after LDLT were higher serum CRP ( $P = 0.006$ ),  $\alpha$ -FP ( $> 1,000$  ng/mL) level at transplantation ( $P < 0.001$ ), beyond Milan criteria ( $P < 0.001$ ), multiple HCC ( $P = 0.042$ ), larger sized tumor ( $>3$  cm) ( $P < 0.001$ ), bilobar distribution ( $P = 0.002$ ), TACE nonresponders ( $P < 0.001$ ), higher tumor grade ( $P = 0.031$ ), vascular invasion ( $P < 0.001$ ), portal vein thrombosis ( $P = 0.047$ ), intrahepatic metastasis ( $P < 0.001$ ), and extrahepatic nodal involvement ( $P = 0.012$ ) (Table 2). Time-related factors including diagnosis-LDLT time ( $P = 0.691$ ), first TACE-LDLT time ( $P = 0.652$ ), and last TACE-LDLT time ( $P = 0.170$ ) were not significant in the univariate analysis for HCC recurrence after LDLT. A multivariate Cox regression analysis also was performed which included the above-mentioned variables which were significant in the univariate analysis. Independent factors for HCC recurrence after LDLT were larger sized tumor ( $>3$  cm) (HR, 2.706; 95% CI, 1.143–6.407;  $P = 0.024$ ), TACE nonresponders (HR, 3.207; 95% CI, 3.217–11.115;  $P = 0.031$ ), microvascular invasion (HR, 4.066; 95% CI, 1.643–10.064;  $P = 0.002$ ), and extrahepatic nodal involvement (HR, 58.68; 95% CI, 5.34–640.62;  $P = 0.001$ ).

### The impact of TACE response on RFS, CSS, and OS for all recipients and within subgroups

Table 3 presents the results from a Cox proportional hazard model showing the influence of TACE response on HCC recurrence and survival in all 134 recipients and subgroups according to TACE numbers and duration of TACE to the time of LDLT. This model was adjusted for independent factors such as larger sized tumor ( $>3$  cm), microvascular invasion, and extrahepatic nodal involvement. For all 134 patients, RFS, CSS, and OS appeared significantly higher in TACE responders ( $n$

$= 73$ ) compared to TACE nonresponders ( $n = 61$ ) (RFS: aHR, 4.199;  $P = 0.005$ ; CSS: aHR, 3.652,  $P = 0.024$ ; OS: aHR, 2.889;  $P = 0.008$ ). In RFS subgroup analysis, subgroups in which TACE responders had higher significant aHR than those of all recipients were single TACE (aHR, 10.281;  $P = 0.031$ ), 12 months or less time from diagnosis to LDLT (aHR, 5.078;  $P = 0.042$ ), 12 months or less time from first TACE to LDLT (aHR, 5.790;  $P = 0.025$ ), and 3 months or less time from last TACE to LDLT (aHR, 6.284;  $P = 0.007$ ). In CSS subgroup analysis, subgroups in which TACE responders had higher significant aHR than those of all recipients were 12 months or less time from first TACE to LDLT (aHR, 4.531;  $P = 0.006$ ), 6 months or less time from last TACE to LDLT (aHR, 4.036;  $P = 0.036$ ), and 3 months or less time from last TACE to LDLT (aHR, 7.033;  $P = 0.016$ ). In OS subgroup analysis, subgroups in which TACE responders had higher significant aHR than those of all recipients were 6 months or less time from last TACE to LDLT (aHR, 3.866;  $P = 0.019$ ), and 3 months or less time from last TACE to LDLT (aHR, 7.055;  $P = 0.005$ ).

### Optimal cutoff timing for LDLT in HCC patients undergoing pre-LT TACE

Of the 134 patients, 29 patients (21.6%) experienced an HCC recurrence. According to the monthly time from last TACE to LDLT, numbers of patients who experienced recurrence after LDLT were distributed as in Fig. 3A. Of 29 patients with HCC recurrence, 25 patients (86.2%) were recipients undergoing TACE 12 months before LDLT. In all patients, the most common time from TACE to LDLT based on HCC recurrence was 2 months – specifically more than 2 months but less than 3 months (Fig. 3A). We divided the 134 patients undergoing TACE prior to LDLT into 2 groups; the group who underwent pre-LT TACE in each month (group A) and the group who did not (group B). The "minimum P-value" approach, which was performed using a log-rank test for comparison of the RFS between groups A and B, was used to determine the best cutoff timing for LDLT after TACE. In all patients, the optimal timing of LDLT after TACE based on the significant difference between groups A and B was 2 months ( $P = 0.022$ ) (Fig. 3A).

In the 73 patient TACE responder group, more than 2 months but less than 3 months after TACE was the best cutoff timing based on the significant difference between groups A and B ( $P = 0.016$ ) (Fig. 3B). However, there was no significant cutoff value between groups A and B according to the log-rank test (Fig. 3C).

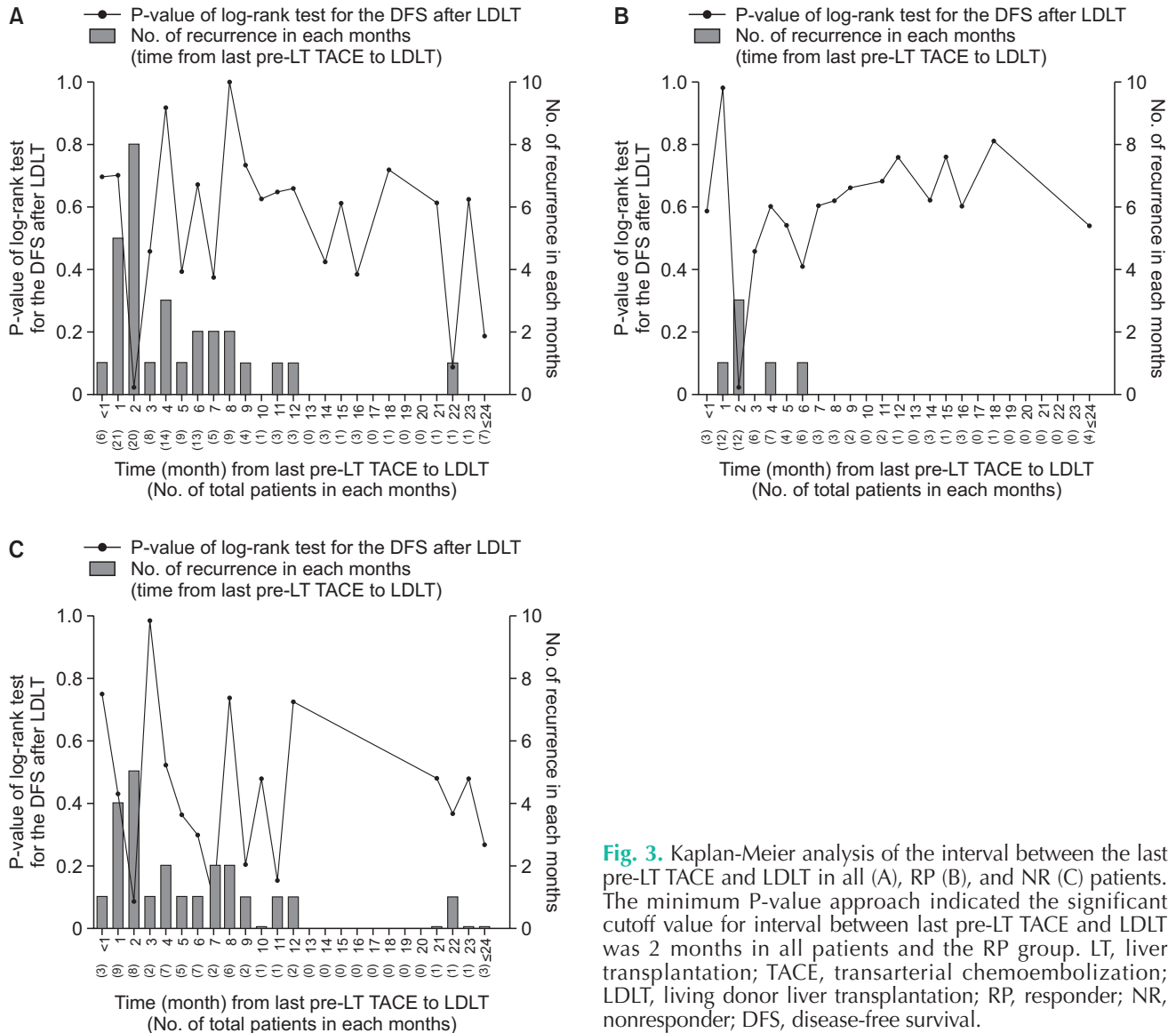
## DISCUSSION

Although the major issue regarding the optimal selection criteria of LT for HCC still remains, LT has become the effective treatment for selected patients with unresectable HCC. TACE is

**Table 3.** Associations of pre-LT TACE response versus nonresponse with recurrence free survival, cancer specific survival, and overall survival in the subgroups based on the number of TACE or the time from clinically critical time to LDLT

Group	No.	Recurrence free survival		Cancer specific survival		Overall survival	
		Unadjusted HR (P-value)	aHR* (P-value)	Unadjusted HR (P-value)	aHR* (P-value)	Unadjusted HR (P-value)	aHR* (P-value)
All recipients	134	5.566 (<0.001)	4.199 (0.005)	5.197 (0.001)	3.652 (0.024)	3.612 (0.001)	2.889 (0.008)
The number of TACE							
Single	42	11.121 (0.024)	10.281 (0.031)	7.525 (0.066)	7.623 (0.075)	3.580 (0.065)	2.127 (0.350)
Multiple	92	4.377 (0.004)	3.742 (0.020)	4.482 (0.008)	3.631 (0.048)	3.508 (0.005)	3.065 (0.020)
Time from HCC Dx. to LDLT (mo)							
≤12	71	6.256 (0.005)	5.078 (0.042)	4.957 (0.015)	3.620 (0.116)	4.201 (0.014)	2.827 (0.129)
>12	63	4.924 (0.015)	2.823 (0.134)	5.249 (0.035)	2.305 (0.336)	2.927 (0.027)	2.927 (0.027)
Time from 1st TACE to LDLT (mo)							
≤12	75	7.051 (0.002)	5.790 (0.025)	5.827 (0.006)	4.531 (0.059)	4.845 (0.005)	3.427 (0.066)
>12	59	3.969 (0.042)	2.757 (0.146)	3.869 (0.099)	2.216 (0.392)	2.653 (0.052)	2.653 (0.052)
Time from last TACE and LT (mo)							
≤6	78	4.262 (0.005)	3.953 (0.018)	4.197 (0.014)	4.036 (0.036)	4.247 (0.005)	3.866 (0.019)
>6	56	11.523 (0.020)	3.966 (0.251)	8.756 (0.042)	1.454 (0.779)	2.780 (0.058)	1.768 (0.343)
Time from last TACE and LT (mo)							
≤3	48	4.509 (0.011)	6.284 (0.007)	5.556 (0.010)	7.033 (0.016)	5.266 (0.005)	7.055 (0.005)
>3	86	8.387 (0.005)	4.926 (0.054)	5.690 (0.025)	2.865 (0.225)	2.916 (0.027)	2.758 (0.037)

LT, liver transplantation; TACE, transarterial chemoembolization; LDLT, living donor liver transplantation; aHR, adjusted hazard ratio; HCC, hepatocellular carcinoma; Dx., diagnosis. \*Models were adjusted for largest tumor >3 cm, microvascular invasion, extrahepatic nodal involvement that were independent factors for HCC recurrence after LDLT in multivariate Cox analysis.



**Fig. 3.** Kaplan-Meier analysis of the interval between the last pre-LT TACE and LDLT in all (A), RP (B), and NR (C) patients. The minimum P-value approach indicated the significant cutoff value for interval between last pre-LT TACE and LDLT was 2 months in all patients and the RP group. LT, liver transplantation; TACE, transarterial chemoembolization; LDLT, living donor liver transplantation; RP, responder; NR, nonresponder; DFS, disease-free survival.

mainly used as bridging therapy for HCC patients awaiting LT to prevent tumor progression and wait-list dropout and improve posttransplant survival [9,10]. In addition, response to TACE has been proposed as an LT biological selection criterion for HCC because it may predict long-term outcome after LT [12-14]. These previous reports' cohorts were mostly patients undergoing DDLT. Thus, the first purpose of this study was to validate the clinical usefulness of the response to pre-LT TACE based on the estimation for risk of recurrence after LT in LDLT recipients. Univariate Cox regression analysis for DFS and OS showed TACE responder groups such as CR or PR showed significantly higher DFS and OS than TACE nonresponder groups such as SD or PD. Multivariate analysis for identification of risk factors affecting recurrence of HCC after LDLT showed nonresponse to TACE prior to LDLT was a significant independent factor as well as larger tumor size, microvascular invasion, and extrahepatic

nodal involvement. This study demonstrated that the response to pre-LT TACE reflected HCC biology and could be used to estimate recurrence even in LDLT recipients in previous studies [12-14,18].

It is well-known that, for HCC patients listed for LT within Milan criteria, a delay LT over 6 to 12 month is a risk factor for tumor aggravation and wait-list dropout or interval dissemination with posttransplant tumor recurrence [9,19]. In most Asian countries that included our Korea, LDLT was developed as a practical alternative to DDLT because of unmet needs such as shortage of deceased donors and strong demand for LT. Determining the timing of LDLT is clinically crucial for HCC patients undergoing local treatment because this timing can be affected by physician subjective decisions as well as strong requests for LDLT. For this reason, we assessed whether LDLT optimal timing could be determined according to the



response to pre-LT TACE. In subgroup analyses adjusted using a Cox proportional hazard model, TACE responders with single TACE had significantly higher aHR than aHR of all recipients. In addition, TACE responders with shorter time-related factors (i.e., diagnosis-LDLT time, first TACE-LDLT time, and last TACE-LDLT time) had significantly higher aHR than all recipients. This indicated that smaller numbers of TACE prior to LDLT and shorter time from TACE to LDLT tended to decrease the risk of recurrence in TACE responders. For recipients with last TACE-LDLT time within 3 months, DFS of responders was 6 fold higher than those of nonresponders. Using the minimum P-value approach with a log-rank test for comparison of the RFS between groups A and B, if last TACE-LDLT time exceeded 2 months, the recurrence rate could be increased significantly in TACE responders. Therefore we suggest that if unresectable HCC patients showed good response to TACE applied as a bridging therapy, LDLT may be performed within 2 months after TACE.

This study's main limitation was its retrospective design. Also, a large number of patients undergoing other treatments

such as RFA and RT were excluded to reduce confounding factors. Also, time-related factors including diagnosis-LDLT time, first TACE-LDLT time, and last TACE-LDLT time were not significantly associated with HCC recurrence after LDLT even in a univariate analysis of all patients. Finally, this study consisted of a small cohort, especially for patients with HCC recurrence. Hence, the minimum P-value approach was not enough to generalize results regarding optimal LDLT timing.

In conclusion, mRECIST-defined TACE response could be used to estimate recurrence of HCC after LDLT in patients undergoing pre-LT TACE. For patients with a good response to TACE, shorter LDLT waiting times after pre-LT TACE may be associated with decreased risk for HCC recurrence after LDLT and increased graft and patient survival.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## REFERENCES

- Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693-9.
- Kim JM, Kwon CH, Joh JW, Kim SJ, Shin M, Kim EY, et al. Patients with unresectable hepatocellular carcinoma beyond Milan criteria: should we perform transarterial chemoembolization or liver transplantation? *Transplant Proc* 2010;42:821-4.
- Kwon CH, Kim DJ, Han YS, Park JB, Choi GS, Kim SJ, et al. HCC in living donor liver transplantation: can we expand the Milan criteria? *Dig Dis* 2007;25:313-9.
- Otto G, Schuchmann M, Hoppe-Lotichius M, Heise M, Weinmann A, Hansen T, et al. How to decide about liver transplantation in patients with hepatocellular carcinoma: size and number of lesions or response to TACE? *J Hepatol* 2013;59:279-84.
- Yang SH, Suh KS, Lee HW, Cho EH, Cho JY, Cho YB, et al. A revised scoring system utilizing serum alphafetoprotein levels to expand candidates for living donor transplantation in hepatocellular carcinoma. *Surgery* 2007;141:598-609.
- Yao FY. Selection criteria for liver transplantation in patients with hepatocellular carcinoma: beyond tumor size and number? *Liver Transpl* 2006;12:1189-91.
- Hwang S, Lee SG, Belghiti J. Liver transplantation for HCC: its role: Eastern and Western perspectives. *J Hepatobiliary Pancreat Sci* 2010;17:443-8.
- Lee SG, Moon DB. Living donor liver transplantation for hepatocellular carcinoma. *Recent Results Cancer Res* 2013;190:165-79.
- Pompili M, Francica G, Ponziani FR, Iezzi R, Avolio AW. Bridging and downstaging treatments for hepatocellular carcinoma in patients on the waiting list for liver transplantation. *World J Gastroenterol* 2013;19:7515-30.
- Terzi E, Ray Kim W, Sanchez W, Charlton MR, Schmeltzer P, Gores GJ, et al. Impact of multiple transarterial chemoembolization treatments on hepatocellular carcinoma for patients awaiting liver transplantation. *Liver Transpl* 2015;21:248-57.
- Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology* 2003;37:429-42.
- Kim DJ, Clark PJ, Heimbach J, Rosen C, Sanchez W, Watt K, et al. Recurrence of hepatocellular carcinoma: importance of mRECIST response to chemoembolization and tumor size. *Am J Transplant* 2014;14:1383-90.
- Millonig G, Graziadei IW, Freund MC, Jaschke W, Stadlmann S, Ladurner R, et al. Response to preoperative chemoembolization correlates with outcome after liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl* 2007;13:272-9.
- Otto G, Herber S, Heise M, Lohse AW, Monch C, Bittinger F, et al. Response to transarterial chemoembolization

- as a biological selection criterion for liver transplantation in hepatocellular carcinoma. *Liver Transpl* 2006;12:1260-7.
15. Vitale A, D'Amico F, Frigo AC, Grigoletto F, Brolese A, Zanus G, et al. Response to therapy as a criterion for awarding priority to patients with hepatocellular carcinoma awaiting liver transplantation. *Ann Surg Oncol* 2010;17:2290-302.
16. Yamamoto Y, Ikoma H, Morimura R, Konishi H, Murayama Y, Komatsu S, et al. Optimal duration of the early and late recurrence of hepatocellular carcinoma after hepatectomy. *World J Gastroenterol* 2015;21:1207-15.
17. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010;30:52-60.
18. Bargellini I, Vignali C, Cioni R, Petruzzi P, Cicorelli A, Campani D, et al. Hepatocellular carcinoma: CT for tumor response after transarterial chemoembolization in patients exceeding Milan criteria--selection parameter for liver transplantation. *Radiology* 2010;255:289-300.
19. Yao FY, Bass NM, Nikolai B, Davern TJ, Kerlan R, Wu V, et al. Liver transplantation for hepatocellular carcinoma: analysis of survival according to the intention-to-treat principle and dropout from the waiting list. *Liver Transpl* 2002;8:873-83.