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Multiple Pretransplant Treatments for Patients Without Pathological Complete Response may Worsen Posttransplant Outcomes in Patients with Hepatocellular Carcinoma

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ABSTRACT

Background. Liver transplant (LT) candidates with hepatocellular carcinoma (HCC) often receive cancer treatment before transplant. We investigated the impact of pre-transplant treatment for HCC on the risk of posttransplant recurrence.

Methods. Adult HCC patients with LT at our institution between 2013 and 2020 were included. The impact of pre-LT cancer treatments on the cumulative recurrence was evaluated, using the Gray and Fine-Gray methods adjusted for confounding factors. Outcomes were considered in two ways: 1) by pathologically complete response (pCR) status within patients received pre-LT treatment; and 2) within patients without pCR, grouped by pre-LT treatment as A) none; B) one treatment; C) multiple treatments.

Results. The sample included 179 patients, of whom 151 (84%) received pretreatment and 42 (28% of treated) demonstrated pCR. Overall, 22 (12%) patients experienced recurrence. The 5-year cumulative post-LT recurrence rate was significantly lower in patients with pCR than those without pCR (4.8% vs. 19.2%, $P = 0.03$). In bivariable analyses, pCR significantly decreased risk of recurrence. Among the 137 patients without pCR (viable HCC in the explant), 28 (20%) had no pretreatment (A), 70 (52%) had one treatment (B), and 39 (20%) had multiple treatments (C). Patients in Group C had higher 5-year recurrence rates than those in A or B (39.6% vs. 8.2%, 6.5%, $P = 0.004$ and $P < 0.001$, respectively). In bivariable analyses, multiple treatments was significantly associated with recurrence.

Conclusions. pCR is a favorable prognostic factor after LT. When pCR was not achieved by pre-LT treatment, the number of treatments might be associated with post-LT oncological prognosis.

Hepatocellular carcinoma (HCC) has a high recurrence rate after curative-intent hepatectomy.[1] Intrahepatic recurrence is the most common presentation, accounting for more than 70% of cases.[2] HCC patients with United Network for Organ Sharing (UNOS) classification T2 disease (solitary lesion <5.0 cm, within 3 lesions < all 3.0 cm) may be candidates for liver transplantation (LT), which decreases risk of recurrence among patients without major vascular invasion or extrahepatic metastases.[3–5] Five-year, overall survival rates may reach 70-90% in appropriately selected cases.[6] Despite the favorable oncologic outcomes of LT for HCC, its widespread use as a treatment option is relatively limited due to donor shortage and disease progression during waitlist time[7]; to prevent drop-out secondary to disease progression during waiting time, LT candidates with HCC often receive treatment, such as resection, ablation, or chemotherapy.[8]

According to a recent, multicenter study, patients who achieved pathological complete response (pCR) after pre-LT locoregional therapies showed significantly lower rates of recurrence and superior survival.[9] Other single-center studies suggested that pCR was associated with improved post-LT outcomes.[10–12] However, the impact of these

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treatments on post-LT outcomes in patients who could not achieve pCR is debatable. We compared the post-LT outcomes between patients with and without pCR and to assess an impact of the number of pre-LT treatment on post-LT outcomes.

METHODS

Study Population

Henry Ford Health System (HFHS) is an integrated tertiary care center in metropolitan Detroit, Michigan. Study protocols were approved by the HFHS Institutional Review Board (#15052); requirements for written, informed consent were waived due to the deidentified and observational nature of data. Retrospective medical records data were collected for patients who received a liver transplant for HCC between January 2013 and December 2019. Adult patients (≥18 years) with HCC identified by pathology in their explants or pre-LT biopsy were eligible for inclusion. Patients with HCC mixed with cholangiocarcinoma, and those receiving retransplant or combined transplant with thoracic organs, intestine, and/or pancreas were excluded. One patient who experienced intraoperative death was excluded (Supplementary Fig. 1). To assess the impact of pre-LT treatment on post-LT recurrence in patients with HCC, two overlapping study samples were created. The first sample included patients who received anticancer treatment for HCC before transplant. The second sample included patients who showed viable HCC in their explants (i.e., patients who did not receive anti-cancer treatment or failure to achieve pCR).

Covariates

Categorical variables included: recipient sex; etiology of end-stage liver disease (hepatitis B virus [HBV], hepatitis C virus [HCV], nonalcoholic steatohepatitis [NASH], cholestatic disease, alcohol-related liver disease); presence of severe/moderate grade ascites; grade III/IV encephalopathy, type of pre-LT treatment (transcatheter arterial chemoembolization [TACE], Yttrium-90 [Y90], ablation, liver resection, external radiation therapy, systemic chemotherapy), presence of pCR in explants, tumor number (single or multiple), vascular invasion, type of liver transplant (deceased or living donor liver transplantation [LDLT]), receipt model for end-stage liver disease (MELD) exception points, HCC criteria (Milan criteria,[13] University of California San Francisco (UCSF) criteria,[14] up to 7 criteria,[15] Japanese 5-5-500 criteria[16]), and use of donation after circulatory death (DCD) donor liver graft.

Continuous variables were classified as the following multilevel categorical variables: recipient serum albumin at transplant (<2.8 g/dl [33rd percentile], 2.8-3.5 g/dl [34–65th percentile], and >3.5 g/dl [66th percentile]); recipient MELD score without exception points at transplant (6–14, 15–29, and ≥30); maximum AFP from HCC diagnosis (<200 ng/ml, 200–1000 ng/ml, and >1,000 ng/ml); AFP at LT (<200 ng/ml, 200–1,000 ng/ml, and >1000 ng/ml); AFP response (low AFP [AFP persistently <200 ng/ml from time of HCC diagnosis]; Responder [maximum AFP 200-1,000 ng/ml to <200 ng/ml at LT, or maximum AFP >1,000 ng/ml to <1,000 ng/ml at LT (must be >50% drop)]; Nonresponder [maximum AFP 200–1000 ng/ml to >200 ng/ml at LT, or maximum AFP >1,000 ng/ml to AFP >1,000 ng/ml at LT])[17]; the number of pretransplant treatments for HCC (none, one, or multiple); and cold ischemia time (<6.0 h, 6.0–7.9 h, or ≥8 h). Additional multilevel categorical variables included: tumor differentiation (well, moderate, or poor); Karnofsky score at transplant (10–30%, 40–60%, or 70–100%); and donor cause of death (trauma, anoxia, cerebrovascular accident [CVA], or other). Age, body mass index (BMI), tumor size, and amount of blood loss at transplant were used as continuous variables. All covariates except presence of pCR in explants, tumor size and number, vascular invasion, and tumor differentiation were collected before or at LT.

Aim 1: Impact of pCR on Post-LT HCC Recurrence Among Patients Who had pre-LT Treatment

Patients who received pre-LT treatment for HCC were classified into two groups: pCR and non-pCR. pCR was defined as the absence of any viable tumor in their explants (if patients had multiple tumors, 100% necrosis was confirmed in all tumors). Patient characteristics and cumulative incidence of recurrence and overall survival after LT were compared between the two groups. Multivariable analysis was performed to investigate the most favorable pre-LT treatment method for pCR using logistic regression. Univariable analyses for risk factors (including pCR) for recurrence was performed, followed by bivariable analysis between pCR and other significant risk factors.

Aim 2: Impact of Number of Pre-LT Treatments and AFP Response on Post-LT Recurrence in Patients Without pCR

Patients with viable HCC in their explants were classified to three groups according to the number of pre-LT treatments for HCC: none (group A); one (group B); or multiple (group C). AFP response was categorized as above. Patient characteristics, cumulative incidence of recurrence, and overall survival post-LT were compared

between each treatment number group. We performed univariable analyses of risk factors for post-LT recurrence, including the number of pre-LT treatments for HCC or AFP response, followed by bivariable analysis between the number of pre-LT treatments or AFP response and other significant risk factors.

Statistical Analysis

Patient and donor characteristics were reported by group. Descriptive statistics for these variables included median and interquartile range (IQR) for continuous variables and numbers and percentages for categorical variables. Continuous variables were compared with the Mann-Whitney *U* test and categorical variables were compared using the chi-square test. Logistic regression was used for the multivariable analysis to identify the optimal pCR treatment method. Post-transplant patient survival was evaluated using the Kaplan-Meier method and groups compared using log-rank tests. Cumulative incidence of recurrence was evaluated using the cumulative incidence function and groups compared using the Gray test. The Fine-Gray method was used to create the univariable and bivariable models for analysis of recurrence. Patient death and HCC recurrence were considered as competing risk events.[18] *P* values <0.05 was considered statistically significant for all analyses. All statistical analyses were completed using SPSS version 27 (IBM, Chicago, IL) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics and Outcomes in the Entire Cohort

A total of 179 patients were eligible for this study (Supplementary Fig. 1). Pre-LT treatments included: 28 (16%) none; 92 (51%) one; and 59 (33%) multiple (Supplementary Table 1). There were 233 total treatments among the 151 pre-LT treated patients (minimum: 1; maximum: 5). The most common pre-LT treatment was transcatheter arterial chemoembolization (TACE), which was administered 118 times (51%); liver resection was performed only 5 times (2%; Supplementary Table 2). Six patients had a peak AFP >1,000 ng/ml (3%), and no patients had an AFP at LT >1,000 ng/ml. Forty-two patients (24%) achieved pCR.

The 1-, 3-, and 5-year cumulative incidence of post-LT HCC recurrence were 5.7% (95% confidence interval [CI] 2–9%), 10.0% (95% CI 6–15%), and 12.9% (95% CI 8–18%), respectively (Supplementary Fig. 2a). The 1-, 3-, and 5-year overall post-LT survival rates were 93.7% (95% CI 89–96%), 86.1% (95% CI 79–90%), and 78.8% (95% CI 70–84%) respectively (Supplementary Fig. 2b).

The proportions of patients who showed beyond transplant criteria at initial diagnosis were 35% (Milan criteria), 31% (UCSF criteria), 13% (Up to 7 criteria), and 17% (5-5-500 criteria) (Supplementary Table 1). Downstaging rates (the number of patients who showed within transplant criteria at LT divided by those of patients who showed beyond transplant criteria at initial diagnosis were 35% (Milan criteria), 53% (UCSF criteria), 39% (up to 7 criteria), and 58% (5-5-500 criteria), respectively (Supplementary Table 3).

Compared with patients who showed within transplant criteria at both initial diagnosis and LT, the cumulative incidence of post-LT HCC recurrence was significantly higher in patients who showed beyond transplant criteria at both initial diagnosis and LT ($P < 0.001$ in each criteria) (Supplementary Fig. 3). There was no statistical difference between patients who showed within transplant criteria at both initial diagnosis and LT and patients who showed downstaging ($P = 0.24$ in Milan criteria, $P = 0.10$ in UCSF criteria, $P = 0.74$, and $P = 0.22$ in 5-5-500 criteria.

Aim 1: Impact of pCR on Post-LT HCC Recurrence Among Patients Who had pre-LT Treatment

Among 151 patients who received pre-LT treatment for HCC, 42 demonstrated pCR, and 109 did not (non-pCR). A larger proportion of the pCR group had serum albumin levels >3.5 g/dl compared with the non-pCR group (48% vs. 28%, $P = 0.03$) and cold ischemia time <6.0 h (91% vs. 72%, $P = 0.04$; Table 1). In multivariable analysis, the treatments most strongly associated with pCR were Y90 (odds ratio [OR] 3.60, 95% CI 1.23-10.50, $P = 0.01$) and ablation (OR 2.97, 95% CI 1.07-8.19, $P = 0.03$; Table 2). Among patients who showed beyond Milan criteria at the initial diagnosis (n = 62), the number of patients who received Y90 was 13 and those who showed pCR was 6 (pCR rate was 46.2%) (TACE; 19.5% [8/41], ablation 6.3% [1/16], radiation 25.0% [1/4], systemic 0% [0/6]; $P = 0.06$).

Two pCR patients had recurrence. Cumulative incidence of post-LT recurrence was lower in the pCR group than the non-pCR groups (1-, 3-, and 5-year: 4.8%, 4.8%, and 4.8% vs. 9.3%, 15.4%, and 19.2%, respectively, $P = 0.03$; Fig. 1a). Overall post-LT survival rates were higher in the pCR group than the non-pCR group but not significantly (Fig. 1b). The unadjusted risk of recurrence was significantly lower in the pCR group compared to the non-pCR group (subdistribution hazard ratio [sHR] 0.22, 95% CI 0.05-0.98, $P = 0.04$). In bivariable analysis adjusted for recurrence risk factors identified in univariable analysis,

TABLE 1 Comparison of characteristics of liver transplant recipients with or without pCR among patients who received pre-LT treatment for hepatocellular carcinoma

Characteristics	Group	pCR N = 42	Non-pCR N = 109	*P*
Recipient age (yr), median [IQR]		60 [55, 64]	62 [59, 65]	0.14
Recipient gender, n (%)	Male	27 (64)	83 (76)	0.20
	Female	15 (36)	26 (24)	
Recipient BMI (kg/m^2), median [IQR]		27.5 [25.3, 30.8]	28.7 [25.0, 32.4]	0.50
HBV, n (%)		0 (0)	2 (2)	0.92
HCV, n (%)		28 (67)	66 (61)	0.61
NASH, n (%)		4 (10)	21 (19)	0.23
Alcohol, n (%)		12 (29)	28 (26)	0.87
Cholestatic disease, n (%)		1 (2)	2 (2)	1.00
Multiple pre-LT treatments, n (%)		20 (48)	39 (36)	0.25
Pre-LT treatment, n (%)	TACE	22 (52)	78 (72)	**0.04**
	Y90	12 (29)	17 (16)	0.11
	Ablation	20 (48)	31 (28)	**0.04**
	Liver resection	1 (2)	4 (4)	1.00
	Radiation	3 (7)	8 (7)	1.00
	Systemic	2 (5)	7 (6)	0.99
LDLT, n (%)		2 (5)	6 (6)	1.00
Exception, n (%)		33 (79)	81 (74)	0.73
Albumin (g/dl), n (%)	>3.5	20 (48)	31 (28)	**0.03**
	2.8–3.5	17 (41)	47 (43)	
	<2.8	5 (12)	31 (28)	
MELD score, n (%)	6-14	27 (64)	62 (57)	0.47
	15-29	12 (29)	42(39)	
	>29	3 (7)	5 (5)	
Karnofsky score (%), n (%)	70–100	4 (10)	9 (8)	0.93
	40–60	34 (81)	91 (84)	
	10–30	4 (10)	9 (8)	
Severe/moderate ascites, n (%)		6 (14)	14 (13)	1.00
Grade III/IV encephalopathy, n (%)		2 (5)	4 (4)	1.00
AFP at LT (ng/ml), n (%)	<200	41 (98)	105 (96)	1.00
	200-1,000	1 (2)	4 (4)	
	>1000	0 (0)	0 (0)	
Peak AFP (ng/ml), n (%)	<200	37 (88)	93 (85)	0.75
	200-1000	3 (7)	12 (11)	
	>1000	2 (5)	4 (4)	
AFP response, n (%)	Low AFP	37 (88)	93 (85)	0.85
	Responder	3 (7)	11 (10)	
	Nonresponder	2 (5)	5 (5)	
Amount of blood loss at LT (ml), median [IQR]		1000 [800, 1657]	1550 [1000, 3000]	**0.01**
Recurrence, n (%)		2 (5)	20 (18)	0.06
Death, n (%)		3 (7)	20 (18)	0.14
Donor age (year), median [IQR]		38 [27, 54]	43 [30, 56]	0.28
Donor gender, n (%)	Male	29 (69)	64 (59)	0.32
	Female	13 (31)	45 (41)	
Cold ischemia time (hours), n (%)	< 6.0	38 (91)	78 (72)	**0.04**
	6.0–7.9	3 (7)	26 (24)	

Table 1 (continued)

Characteristics	Group	pCR N = 42	Non-pCR N = 109	*P*
	≥ 8.0	1 (2)	5 (5)	
DCD donor, n (%)		6 (14)	11 (10)	0.65
Donor cause of death, n (%)	Trauma	18 (43)	38 (35)	0.61
	Anoxia	8 (19)	32 (29)	
	CVA	13 (31)	31 (28)	
	Others	3 (7)	8 (7)	

Bold denotes statistically significant *P* values < 0.05

AFP alpha-fetoprotein; *BMI* body mass index; *CVA* cerebrovascular accident; *DCD* donation after circulatory death; *HBV* hepatitis B virus; *HCC* hepatocellular carcinoma; *HCV* hepatitis C virus; *LDLT* living donor liver transplantation; *LT* liver transplant; *MELD* model for end-stage liver disease; *NASH* nonalcoholic steatohepatitis; *pCR* pathological complete response; *TACE* transcatheter arterial chemoembolization; *Y90* Yttrium-90

Data were summarized by using the median with interquartile range (IQR) for continuous variables and by using percentage for discrete variables. Continuous variables were analyzed using the Mann-Whitney *U* test and discrete variables were analyzed using a chi-square test

TABLE 2 Impact of pre-LT treatment for hepatocellular carcinoma on pCR

	OR	95% CI	*P*
TACE	0.92	0.35–2.42	0.87
Y90	3.60	1.23–10.50	**0.01**
Liver resection	0.68	0.06–7.68	0.76
Ablation	2.97	1.07–8.19	**0.03**
Systemic	0.60	0.10–3.36	0.56
Radiation	0.63	0.14–2.82	0.55

Bold denotes statistically significant *P* values < 0.05

LT liver transplant; *pCR* pathological complete response; *TACE* transcatheter arterial chemoembolization; *Y90* Yttrium-90

pCR patients had a significantly lower risk of recurrence (Table 3).

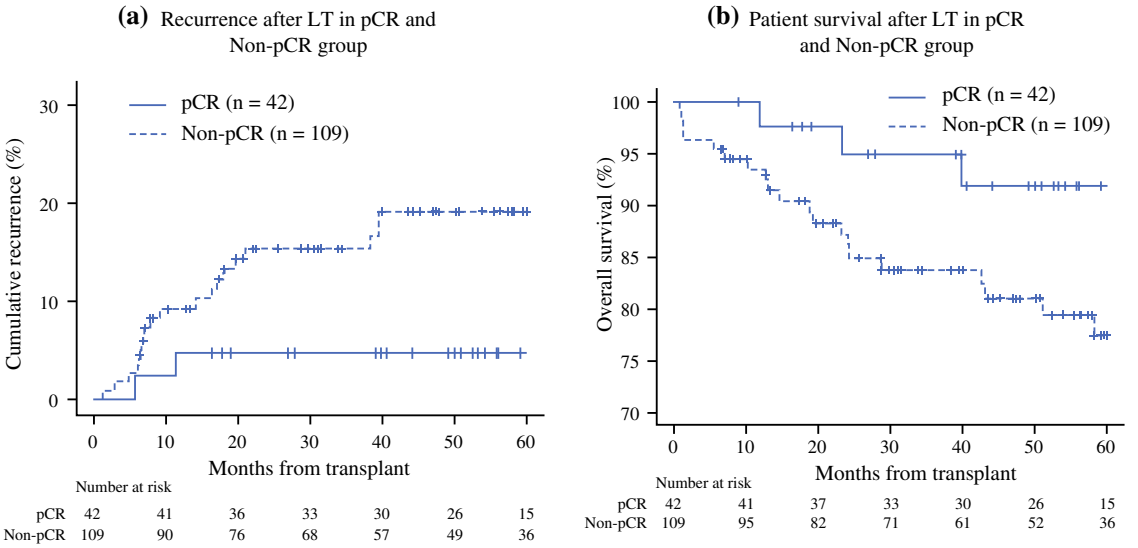
Aim 2: Impact of the Number of Pre-LT Treatments and AFP Response on Post-LT Recurrence in Patients Without pCR

Of the 137 patients who had viable HCC in their explants, 28 were as group A (no pre-LT treatments), 70 were group B (1 treatment), and 39 were group C (multiple treatments). As shown in Table 4, group A patients had the lowest rate of HCC exception points (4%, 70%, and 82%, for groups A, B, and C, respectively, $P < 0.001$). Group C had the highest proportion of multiple tumors (39%, 37%, and 74% for groups A, B, and C, respectively, $P = 0.001$). Patients in group C had the highest rate of exceeding up-to-7 criteria (4%, 11%, and 26% for groups A, B, and C, respectively, $P = 0.02$), and 5-5-500 criteria (0%, 7%, and 18%, for groups A, B, and C, respectively, $P = 0.03$).

The cumulative incidence of post-LT HCC recurrence was highest in Group C (1-, 3-, and 5-year: 0%, 3.9%, and 8.2% in group A; 0%, 4.6%, and 6.5% in group B; and 21.1%, 30.5%, and 39.6% in group C, respectively; group A vs. C, $P = 0.004$; group B vs. C, $P < 0.001$; Fig. 2a). Overall post-LT survival rates in group C were significantly lower than those in group B (1-, 3-, and 5-year: 97.1%, 92.4%, and 85.3% in group B, 86.5%, 66.4%, and 61.3% in group C, $P = 0.002$) but similar to group A ($P = 0.43$; Fig. 2b).

Unadjusted risk of recurrence was significantly higher in Group C compared to Group A (sHR 6.79, 95% CI 1.61–28.63, $P = 0.009$). Those in groups A and B were similar. Bivariable analysis adjusted for recurrence risk factors identified in the univariable analysis showed that receipt of multiple treatments (group C) was associated with significantly higher risk of recurrence with any of combination of other significant factors (Table 5). Also, prolonged cold ischemia time (≥8.0 h) was significantly associated with recurrence of HCC compared with cold ischemia time <6.0 h.

Of the 137 patients who had viable HCC in their explants, 121 were classified as Low AFP, 12 as Responders, and 4 as Nonresponders. The cumulative incidence of post-LT recurrence in Nonresponders after pre-LT treatment(s) was significantly higher than in those with Low AFP or Responders (1-, 3-, and 5-year: 3.4%, 9.9%, and 13.4% [Low AFP]; 8.3%, 8.3%, and 17.6% [Responders]; 75.0%, 75.0%, and 75.0% [Nonresponders]; Low AFP vs. Nonresponders, $P < 0.001$; Responders vs. Nonresponders, $P = 0.03$; Fig. 2c). In univariable analysis, Nonresponders showed significantly higher risk for HCC recurrence compared with Low AFP (sHR 11.22, 95% CI 2.44-51.52, $P = 0.001$). Risk of post-LT recurrence in Nonresponder status was assessed in a bivariable model, which revealed



Year	Recurrence rate (%)		P
	pCR	Non-pCR	
1-year	4.8	9.3	0.03
3-year	4.8	15.4	
5-year	4.8	19.2	

Year	Overall survival rate (%)		P
	pCR	Non-pCR	
1-year	97.6	93.5	0.06
3-year	94.9	83.8	
5-year	91.9	77.5	

FIG. 1 Comparison of post-LT outcome between pCR and non-pCR groups. **a** Cumulative recurrence rates after LT in group pCR were significantly lower than those in group non-pCR (1-, 3-, and 5-year: 4.8%, 4.8%, and 4.8% in patients who achieved pCR; 9.3%, 15.4%, and 19.2% in non-pCR patients, respectively, $P = 0.03$). **b** Overall patient survival rates after LT in patients who achieved pCR; there was no statistically significant difference compared with those without pCR (1-, 3-, and 5-year: 97.6%, 94.9%, and 91.9% vs. 93.5%, 83.8%, and 77.5%, respectively, $P = 0.06$)

TABLE 3 Risk factors for HCC recurrence after liver transplantation among patients with pre-LT treatment for hepatocellular carcinoma

Variables	aHR (95% CI)	*P*	pCR (Ref. non-pCR) aHR (95% CI)	*P*
Bivariate analysis with pCR for factors associated with recurrence				
Recipient gender, male	3.54 (0.88–14.21)	0.07	0.22 (0.05–0.98)	**0.04**
MELD score ≥30 (Ref. 6–14)	3.13 (1.04–9.34)	**0.04**	0.21 (0.04–0.95)	**0.04**
Multiple treatments (Ref. one treatment)	5.97 (2.43–14.69)	< **0.001**	0.17 (0.04–0.77)	**0.02**
AFP at LT 200–1000 ng/ml (Ref. <200 ng/ml)	8.65 (1.98–37.65)	**0.004**	0.21 (0.04–0.95)	**0.04**
Maximum AFP >1,000 ng/ml (Ref. <200 ng/ml)	4.57 (1.15–18.10)	**0.03**	0.22 (0.05–0.99)	**0.04**
AFP nonresponder (Ref. Low AFP)	15.13 (3.95–57.92)	< **0.001**	0.24 (0.06–0.85)	**0.02**

Bold denotes statistically significant P values < 0.05

AFP alpha-fetoprotein; *aHR* adjusted hazard ratio; *HCC* hepatocellular carcinoma; *LT* liver transplant; *MELD* model for end-stage liver disease; *pCR* pathological complete response.

that nonresponse was a significant risk factor for recurrence (Supplementary Table 4).

DISCUSSION

In a sample of 179 HCC patients who underwent liver transplant, we found that patients who achieved pCR had significantly lower post-LT HCC recurrence compared to those without pCR. Patients who could achieve down-staging showed similar post-LT outcomes compared with

TABLE 4 Comparisons of characteristics of patients according to the number of pre-LT treatment for hepatocellular carcinoma among patients who showed viable HCC in their explants

Characteristics	Group	Group A N = 28	Group B N = 70	Group C N = 39	*P*
Recipient age (yr), median [IQR]		61 [56, 63]	62 [58, 65]	64 [60, 67]	0.12
Recipient gender, n (%)	Male	23 (82)	52 (74)	31 (80)	0.65
	Female	5 (18)	18 (26)	8 (20)	
Recipient BMI (kg/m^2), median [IQR]		28.8 [26.9, 33.0]	29.1 [25.6, 32.8]	27.1 [24.5, 31.9]	0.29
HBV, n (%)		1 (4)	1 (1)	1 (3)	0.79
HCV, n (%)		16 (57)	45 (64)	21 (54)	0.53
NASH, n (%)		7 (25)	12 (17)	9 (23)	0.60
Alcohol, n (%)		9 (32)	18 (26)	10 (26)	0.79
Cholestatic disease, n (%)		0 (0)	2 (3)	0 (0)	0.37
LDLT, n (%)		2 (7)	4 (6)	2 (5)	0.94
Exception, n (%)		1 (4)	49 (70)	32 (82)	**<0.001**
Albumin (g/dl), n (%)	> 3.5	4 (14)	17 (24)	14 (36)	0.06
	2.8-3.5	12 (43)	36 (51)	11 (28)	
	< 2.8	12 (43)	17 (24)	14 (36)	
MELD score, n (%)	6-14	5 (18)	43 (61)	20 (51)	**< 0.001**
	15-29	16 (57)	23 (33)	18 (46)	
	> 29	7 (25)	4 (6)	1 (3)	
Karnofsky score (%), n (%)	70-100	2 (7)	8 (11)	1 (3)	0.15
	40-60	20 (71)	56 (80)	35 (90)	
	10-30	6 (21)	6 (9)	3 (8)	
Severe/moderate ascites, n (%)		11 (39)	10 (14)	4 (10)	**0.005**
Grade III/IV encephalopathy, n (%)		6 (21)	3 (4)	1 (3)	**0.005**
AFP at LT (ng/ml), n (%)	< 200	28 (100)	68 (97)	37 (95)	0.46
	200-1000	0 (0)	2 (3)	2 (5)	
	> 1000	0 (0)	0 (0)	0 (0)	
Peak AFP (ng/ml), n (%)	< 200	28 (100)	60 (86)	33 (85)	0.27
	200-1000	0 (0)	8 (11)	4 (10)	
	> 1000	0 (0)	2 (3)	2 (5)	
AFP response, n (%)	Low AFP	28 (100)	60 (86)	33 (86)	0.27
	Responder	0 (0)	8 (11)	4 (10)	
	Nonresponder	0 (0)	2 (3)	2 (5)	
Maximum tumor size (cm), median [IQR]		2.1 [1.5, 2.6]	2.4 [1.5, 3.4]	2.2 [1.8, 3.0]	0.48
Multiple tumors, n (%)		11 (39)	26 (37)	29 (74)	**0.001**
Vascular invasion, n (%)		1 (4)	5 (7)	6 (15)	0.19
Differentiation, n(%)	Well	7 (25)	25 (36)	6 (15)	0.21
	Moderate	19 (68)	40 (57)	28 (72)	
	Poor	2 (7)	5 (7)	5 (13)	
Amount of blood loss at LT (ml), median [IQR]		1,000 [625, 3,275]	1850 [1000, 3000]	1200 [950, 2,500]	0.52
Beyond Milan criteria, n (%)		5 (18)	20 (29)	16 (41)	0.11
Beyond UCSF criteria, n (%)		3 (11)	12 (17)	12 (31)	0.09
Beyond up to 7 criteria, n (%)		1 (4)	8 (11)	10 (26)	**0.02**
Beyond 5-5-500 (Japanese) criteria, n (%)		0 (0)	5 (7)	7 (18)	**0.03**
Recurrence, n (%)		2 (7)	5 (7)	13 (33)	**< 0.001**
Death, n (%)		8 (29)	8 (11)	12 (31)	**0.02**
Donor age (yr), median [IQR]		35 [28, 48]	43 [30, 55]	44 [28, 56]	0.43

Table 4 (continued)

Characteristics	Group	Group A N = 28	Group B N = 70	Group C N = 39	*P*
Donor gender, n (%)	Male	19 (68)	40 (57)	25 (64)	0.56
	Female	9 (32)	30 (43)	14 (36)	
Cold ischemia time (hr), n (%)	<6.0	21 (75)	50 (71)	28 (72)	0.93
	6.0-7.9	6 (21)	16 (23)	10 (26)	
	≥8.0	1 (4)	4 (6)	1 (3)	
DCD donor, n (%)		1 (4)	7 (10)	4 (10)	0.55
Donor cause of death, n (%)	Trauma	15 (54)	24 (34)	14 (36)	0.56
	Anoxia	6 (21)	20 (29)	12 (31)	
	CVA	4 (14)	21 (30)	10 (26)	
	Others	3 (11)	5 (7)	3 (8)	

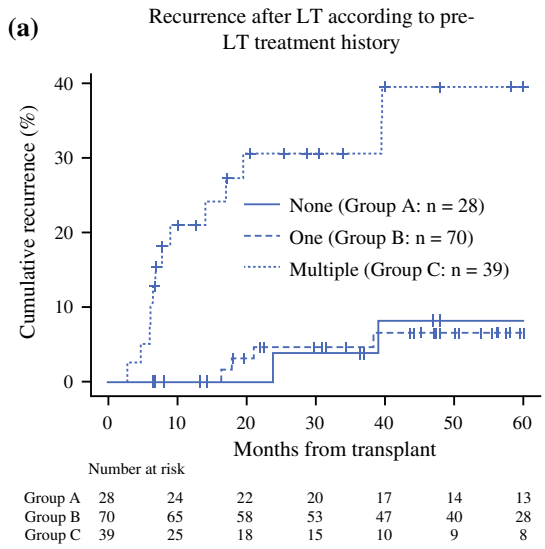
Data were summarized by using the median with interquartile range (IQR) for continuous variables and by using percentage for discrete variables. Continuous variables were analyzed using the Mann Whitney U test and discrete variables were analyzed using a chi-square test

Bold denotes statistically significant P values < 0.05

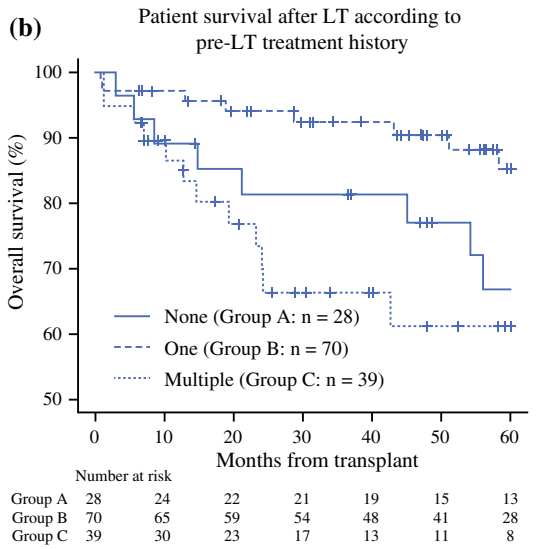
AFP alpha-fetoprotein; *BMI* body mass index; *CVA* cerebrovascular accident; *DCD* donation after circulatory death; *HBV* hepatitis B virus; *HCC* hepatocellular carcinoma; *HCV* hepatitis C virus; *LDLT* living donor liver transplantation; *LT* liver transplant; *MELD* model for end-stage liver disease; *NASH* nonalcoholic steatohepatitis; *pCR* pathological complete response; *UCSF* University of California San Francisco

those who showed within transplant criteria at both initial diagnosis and LT. Among patients with pre-LT treatment, we observed that AFP was associated with risk of recurrence. Nonresponders were more than 11 times more likely to experience recurrence compared with Low AFP patients. Change in AFP before and after treatment could be used as a surrogate marker to predict a risk of post-LT HCC recurrence. These were consistent with the previous reports.[9,17] In addition, a history of multiple pre-LT treatments without pCR was associated with risk of post-LT recurrence of HCC.

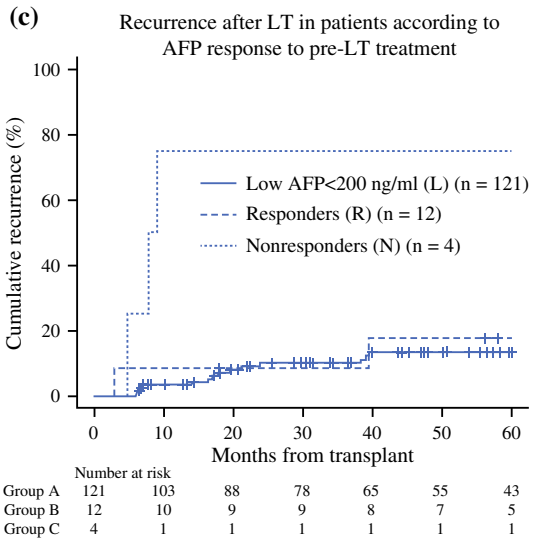
In our cohort, pCR was associated with a lower risk of post-LT recurrence. This is consistent with previous research. DiNorcia et al. analyzed 3,439 patients who received pre-LT locoregional therapy for HCC; they found that patients who demonstrated pCR had lower rates of recurrence compared to without pCR (5 years: 5.8% vs. 16%).[9] Our study also showed that the patients who achieved pCR had significantly lower cumulative recurrence than those without pCR. We found that rates of pCR were highest with Y90 and ablation. While ablation is a well-recognized curative therapy,[19] the indication of ablation therapy is limited to small, nondiffuse tumors, which should not be close to major vasculature.[20,21] Y90 has been reported to be useful for patients with unresectable or recurrent HCC but with fewer adverse events compared with other interventions.[22,23] Salem et al. reported that patients treated with Y90 had a longer time-to-progression and fewer adverse events than those who received TACE for unablatable or unresectable HCC.[22] Recently, Somma et al. reported that complete response rate of 70% after Y90, according to modified Response Evaluation Criteria in Solid Tumors (mRECIST).[23] There are several reports about use of Y90 as a bridging or downstaging therapy prior to LT. One study showed that the downstaging rate was higher in Y90 than in TACE but that post-LT recurrence was similar,[24] whereas another noted that Y90 was associated with lower risk of post-LT recurrence and with presence of microvascular invasion (3.6% in Y90, 27% in TACE).[25] According to the largest single-center study about Y90 prior to LT by Gabr et al., a successful rate of bridging to transplant was 98% and downstaging rate from T3 or 4 to T2 was 47%.[26] In our study cohort, 32 patients received Y90. The proportion of patients who had small tumor (<2 cm) was 25% (n = 8), and the proportion of patients who had single tumor was 38% (n = 12). The maximum tumor size was 9.5 cm, and maximum tumor number was 10. Also, the proportion of patients who showed pCR was 46.2% among patients who received Y90 and showed beyond Milan criteria at the diagnosis. Although it did not reach statistical significance, this rate was higher compared with other modalities. Y90 might be available even for patients who are not suitable candidates for ablation, such as patients beyond Milan criteria. Our results also might support the use of Y90 as an option for pre-LT tumor control.



Year	Recurrence rate (%)			P	
	Group A	Group B	Group C	Group A vs. C	Group B vs. C
1-year	0	0	21.1	0.004	<0.001
3-year	3.9	4.6	30.5		
5-year	8.2	6.5	39.6		



Year	Recurrence rate (%)			P	
	Group A	Group B	Group C	Group A vs. C	Group B vs. C
1-year	89.1	97.1	86.5	0.43	0.002
3-year	81.4	92.4	66.4		
5-year	66.8	85.3	61.3		



Year	Recurrence rate (%)			P	
	L	R	N	L vs. N	R vs. N
1-year	3.4	8.3	75.0	<0.001	0.03
3-year	9.9	8.3	75.0		
5-year	13.4	17.6	75.0		

FIG. 2 Comparison of post-LT outcomes among groups A, B, and C. **a** Cumulative recurrence rates after LT in group C were significantly higher than those in group A or B (1-, 3-, and 5-year: 0%, 3.9%, and 8.2% in group A; 0%, 4.6%, and 6.5% in group B; 21.1%, 30.5%, and 39.6% in group C, respectively; group A vs. C, $P = 0.004$; group B vs. C, $P < 0.001$). **b** Overall patient survival rates after LT in group C were significantly lower than those in group B (1-, 3-, and 5-year: 97.1%, 92.4%, and 85.3% in group B, 86.5%, 66.4%, and 61.3% in group C, respectively; $P = 0.002$) but similar between groups C and A (1-, 3-, and 5-year: 89.1%, 81.4%, and 66.8% in Group A, $P = 0.43$). **c** Cumulative recurrence rates after LT in Nonresponders were significantly higher than those with Low AFP or Responders (1-, 3-, and 5-year: 3.4%, 9.9%, and 13.4% in Low AFP; 8.3%, 8.3%, and 17.6% in Responders; 75.0%, 75.0%, and 75.0% in Nonresponders, respectively; Low AFP vs. Nonresponders, $P < 0.001$; Responders vs. Nonresponders, $P = 0.03$)

TABLE 5 Risk for recurrence after liver transplantation among patients who showed viable HCC in their explants

Variables	aHR (95%CI)	*P*	Multiple (Group C) (Ref. None[Group A]) aHR (95%CI)	*P*
Bivariate analysis for the risk of the number of pre-LT treatment for HCC recurrence				
MELD score ≥30 (Ref. 6-14)	6.49 (1.96–21.45)	**0.002**	12.09 (2.80–52.16)	**< 0.001**
AFP at LT 200-1,000 ng/ml (Ref. <200 ng/ml)	12.21 (3.84–38.77)	**< 0.001**	5.34 (1.25–22.85)	**0.02**
AFP nonresponder (Ref. Low AFP)	12.34 (3.87–39.31)	**< 0.001**	5.28 (1.22–22.69)	**0.02**
Maximum tumor size	1.31 (1.10–1.55)	**0.002**	6.22 (1.46–26.46)	**0.01**
Multiple tumors	2.18 (0.84–5.66)	0.11	5.46 (1.31–22.77)	**0.02**
Vascular invasion	5.10 (1.69–15.39)	**0.003**	5.03 (1.22–20.76)	**0.02**
Beyond Milan criteria	3.40 (1.38–8.36)	**0.007**	5.43 (1.28–23.05)	**0.02**
Beyond UCSF criteria	2.44 (0.99–5.99)	0.05	5.92 (1.40–25.04)	**0.01**
Beyond up to 7 criteria	3.70 (1.43–9.54)	**0.006**	5.07 (1.17–21.96)	**0.03**
Beyond 5-5-500 criteria	5.99 (2.05–17.47)	**0.001**	4.55 (1.03–20.04)	**0.04**
Cold ischemia time ≥ 8.0 h (Ref. < 6.0 h)	5.58 (2.06–15.08)	**< 0.001**	7.34 (2.04–26.34)	**0.002**

Bold denotes statistically significant *P* values < 0.05

AFP alpha-fetoprotein; aHR, adjusted hazard ratio; *HCC* hepatocellular carcinoma; *LT* liver transplant; *MELD* model for end-stage liver disease; *UCSF* University of California San Francisco

We also found that a history of multiple pre-LT treatments was significantly associated with posttransplant recurrence. A U.S. multicenter study of 3,601 patients, who received bridging locoregional therapy, showed that receipt of three or more locoregional therapies was associated with HCC recurrence; need for additional treatments likely represents more aggressive tumor biology.[27] In our study, the recurrence rate in patients with multiple treatments was higher than those with one treatment, whereas the recurrence rate in patients without any pre-LT treatment was similar to those with one treatment. Because patients with multiple pre-LT treatments were more likely to have more advanced tumors, we adjusted for other oncological factors using bivariable models, which confirmed that a history of multiple treatments was an unfavorable factor for recurrence. When LT patients had viable HCC in the explant liver even after pre-LT treatment(s), the number of pre-LT treatment may need to be taken into account for post-LT monitoring for HCC recurrence, because the risk of HCC recurrence associated with multiple treatments in this population was independent of other oncological factors.

Several groups have reported that local HCC recurrence after treatment exhibit more aggressive tumor behavior than treatment-naïve HCC.[28–31] Recurrence after insufficient ablation for HCC resulted in dedifferentiation or higher proportion of vascular invasion.[28,29] An experimental study showed that sublethal heat treatment transforms HCC cells to a progenitor-like, highly proliferative cellular phenotype *in vitro* and *in vivo*.[30] In addition, a previous study reported that the doubling time of recurrent lesions after TACE was shorter than that of the first diagnosed HCC and that the prognosis was worse in cases with a short doubling time.[31] Those findings might account for the association of multiple pre-LT treatments and non-pCR with the higher risk of post-LT HCC recurrence.

In our study, prolonged cold ischemia time was significantly associated with the recurrence of HCC after LT. We previously reported that cold ischemia time >10 h was significantly associated with recurrence of HCC after LT.[32] Ling et al. also reported a similar result in which cold ischemia time < 12 h.[33] Although our cutoff value of cold ischemia time was different from their studies, our result was consistent with these reports. Experimentally, hypoxia facilitates cellular growth, adhesion, and angiogenesis.[34] Ischemia reperfusion injury also impairs the hepatic microcirculatory barrier and activates cell invasion and migration.[35] These might lead to the recurrence of HCC.

There are a number of limitations to our study. This is a retrospective, single-center analysis with a small sample size. Consequently, we could include only two variables in our multivariable analysis. Also, it was not possible to determine whether the administered pre-LT therapy was intended as downstaging or bridging therapy. Despite these limitations, this study provides important insights into the risk stratification for HCC recurrence especially for appropriate post-LT follow-up.

CONCLUSIONS

pCR is associated with lower rates of post-LT recurrence in HCC patients who received pre-LT treatment. Aggressive downstaging prior to LT should be tried. In cases without pCR, if the initial diagnosis is advanced HCC, the indication for transplantation might be carefully considered. To validate our findings, further studies would be warranted. In addition, we found that Y90 was the treatment most likely to be associated with achieving pCR. Because multiple pre-LT treatments and AFP trend are strong risk factors for HCC recurrence among patients who have viable HCC in their explants, these patients should be monitored carefully after LT.

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