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Original Article

Advantage of early liver transplantation whenever indicated for hepatocellular carcinoma recurrence after primary liver resection

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ABSTRACT

Background: Liver transplantation (LT) for recurrent hepatocellular carcinoma (HCC) following liver resection (LR) has been considered a promising strategy for improving patient's outcome. The study aimed to analyse patients from primary LR to LT for HCC and to provide additional information for decision-making in therapeutic strategies for patients with HCC.

Methods: Among 776 LTs, a retrospective analysis of patients who had undergone LT for recurrent HCC after primary LR between May 2005 and 2017 February was performed.

Results: During the follow-up period, the overall recurrence-free survival rates at 1, 3 and 5 years were 84.8%, 68.2% and 68.2%, and disease-specific overall-survival rates were 95.7%, 74.4% and 66.7% at 1, 3 and 5 years after LT, respectively. Beyond University of California at San Francisco (UCSF) transplantation criteria ($p = 0.018$, hazard ratio (HR) = 12.70), maximum tumor size $\geq$ 5 cm at LR ($p = 0.012$, HR = 7.90) and period between post-LR HCC recurrence and LT $\geq$ 1 year ($p = 0.030$, HR = 7.57) were prognostic factors of HCC recurrence after LT. Moreover, HCC recurrence after LT was the solely independent risk factor affecting overall survival of patients.

Conclusion: Large tumor size at LR should be taken into cautious tending to HCC recurrence even after salvage LT. Importantly, LT should be considered as soon as possible preferably within 1 year whenever post-LR recurrent HCC meets transplantation criteria.

Hepatocellular carcinoma (HCC) is one of the most common malignancy and leading cause of cancer-related deaths worldwide. Despite rapidly evolving treatment for HCC, surgical management remains the main option for curative-intent therapy as well as offering the most favourable long-term outcomes [1–4]. Of these, surgical management consists of liver resection (LR) and liver transplantation (LT), and each has its advantages and disadvantages. To our

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At a glance of commentary

Scientific background on the subject

Liver transplantation for post-hepatectomy hepatocellular carcinoma recurrence has been considered a promising strategy for improving patient's outcome. The study showed an outcome analysis for patients with salvage liver transplantation for hepatocellular carcinoma recurrence after primary liver resection.

What this study adds to the field

The study provided additional information for decision-making in therapeutic strategies for patients with hepatocellular carcinoma, in which liver transplantation should be considered as soon as possible preferably within 1 year whenever post-hepatectomy recurrent hepatocellular carcinoma meets transplantation criteria.

knowledge, LR has a higher incidence of cancer recurrence and an inferior survival rate as compared with LT [5–7]. Whereas, LT needs to fight against the shortage of organ availability and life-long immunosuppressant medication. Although selection of either LR or LT for early stage HCC is still a debatable option, the combination of LR followed by LT for late stage liver cirrhosis and/or recurrent HCC has been considered a promising strategy for patients with HCC [8,9].

As a result of improvements in surgical technique and perioperative patient care utilized for LT, it has now become a common and routine operation as foretold by Thomas E. Starzl a few decades ago. Recently, the concept of salvage LT for recurrent HCC after primary LR has been proposed to extend survival time of patients with HCC [8]. Subsequently, numerous experiences regarding the success of salvage LT were widely reported [10–13]. However, studies of outcome and HCC recurrence following LT remain entirely elusive. Moreover, despite a growing experience, predictors related to salvage LT is still an issue of great importance in order to optimise therapeutic strategies for patients with HCC. In the current study, we retrospectively reviewed our experience in patients who had undergone LT for recurrent HCC after primary LR. The study also aimed to examine factors associated with the prognosis and outcome of patients and to provide additional information for decision-making in therapeutic strategies for patients with HCC.

Materials and methods

Patients

A total of 776 consecutive LTs were performed at our institute between May 2005 and February 2017. All medical records of patients were retrospectively reviewed under the approval from the Institutional Review Board. Patients who had undergone LT for post-LR recurrent HCC were enrolled in the current study. As a result, 59 patients including 51 males and 8 females were eligible for analysis of this study. Meanwhile, 590 patients who had HCC recurrence following primary LR during the corresponding period were analysed for survival comparison as well.

Diagnosis and treatment of HCC

Clinically, the diagnosis of HCC was usually based on the diagnostic criteria of the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD). The treatment of HCC mainly consisted of multidisciplinary therapy, including surgical management, locoregional therapies, radiation therapy and systemic chemotherapy or a combination of these treatments. Generally, the selection of treatment modality was determined by the consensus of the institute's liver cancer committee, and LR was always the preferred treatment whenever HCC was considered to be resectable, as previously described [14].

LT was recommended for patients who had advanced liver cirrhosis and/or unresectable HCC, but patients with imaging evidence of extrahepatic metastasis or major vascular invasion were considered unsuitable for LT. HCC patients were placed on the waitlist only if imaging evidence of tumor status met the proposed criteria from the University of California at San Francisco (UCSF) [3] and in patients up to 70 years old. After LT, the explanted liver were thoroughly examined to determine the pathologic characteristics of HCC. All statistical analysis of variables regarding tumor characteristics were performed according to the pathological examination of the hepatic specimens obtained from LR and LT in this study.

Postoperative follow-up

Generally, the surveillance of patients after operation was similar for LR and LT. All patients were regularly followed for HCC recurrence by measurement of serum α-fetoprotein (AFP) and liver ultrasonography at monthly intervals in the initial 3 months and every 3 months thereafter until death or the end of the present study. Radiologic examinations including computed tomography (CT) and/or magnetic resonance imaging (MRI), were performed annually or whenever suspicious of HCC recurrence in patients after LR. However, radiologic imaging was routinely arranged at 3, 6, 12 months and every year afterward following LT.

Statistical analysis

The primary variables, including demographics and clinicopathologic features of LR and LT, were assessed to determine the prognostic factors. The Cox proportional hazards regression model was applied to identify the factors that influence HCC recurrence after LT, and all the significant factors with a p value of less than 0.1 from univariate analysis were further analysed by multivariate analysis in a forward stepwise manner. Recurrence-free survival (RFS) was defined by the date of LR or LT to the date of detecting HCC recurrence. Overall survival (OS) was measured from the date of LR or LT to the date of death or until the end of this study. Survival curves were constructed by the Kaplan–Meier method and further compared by the log rank test. All the data were analysed using the statistical software SPSS version 20.0 (IBM Inc.,

Table 1 Clinicopathologic characteristics of patients.

Characteristics	No. of patient (%)
Sex (Male:Female)	51:8
Hepatitis status	
Hepatitis B positive	48 (81.4%)
Hepatitis C positive	6 (10.2%)
Non-B and Non-C	5 (8.4%)
Primary liver resection	
Age at LR (years), median (range)	50 (26–68)
Tumor nodule	
Single	51 (86.4%)
Multiple	8 (13.6%)
Maximum tumor size, median (range)	2.5 (1.0–10.0)
Extent of liver resection	
≥3 segment	14 (23.7%)
<3 segment	45 (76.3%)
Period of LR to LT (months), median (range)	44.2 (3.5–180.6)
Period of post-LR HCC recurrence to LT (months)	11.0 (1.0–174.0)
Locoregional therapy before LT	
Yes	
Bridging therapy	46 (78.0%)
Down-staging intent	5 (8.4%)
No	8 (13.6%)
Liver transplantation	
Age at LT (years), median (range)	54 (32–68)
MELD score, median (range)	9 (5–28)
AFP (ng/ml), median (range)	13.9 (1.3–2181)
Type of LT	
DDLT	12 (20.3%)
LDLT	47 (79.7%)
Pathologic tumor characteristics	
Tumor Number, median (range)	2 (1–29)
Maximum tumor size, median (range)	2 (1.0–8.3)
UCSF criteria (within:beyond)	46:13
HCC recurrence	15 (25.4%)
Outcomes	
Alive and HCC free	36 (61.0%)
Alive with recurrent HCC	3 (5.1%)
Died of HCC	12 (20.3%)
Died of other causes	5 (8.5%)
Hospital Mortality	3 (5.1%)

Abbreviations: LR: liver resection; HCC: hepatocellular carcinoma; LT: liver transplantation; MELD: Model for End-stage Liver Disease; AFP: alpha-fetoprotein; DDLT: deceased donor liver transplantation; LDLT: living donor liver transplantation.

Armonk, NY, USA) for Windows. A p value of less than 0.05 was defined as statistically significant.

Results

Clinical features of patients

The clinical features of the patients with primary LR for HCC followed by LT are summarized in [Table 1]. Hepatitis B virus-related cirrhosis and HCC remain the main aetiology of patients that accounted for 81.4% in this study. With regard to primary LR, the majority of patients had a single tumor (86.4%) and underwent LR less than 3 Couinaud's segments (76.3%). Six patients underwent LR twice due to HCC recurrence after the first LR. The median time from the last LR to LT was 44.2 months (range 3.5–180.6 months), and the median period of post-LR HCC recurrence to LT was 11.0 months (range 1.0–174 months). Before LT, locoregional therapy was performed for post-LR recurrent HCC in 51 patients that consisted of 46 patients for bridging therapy and 5 patients for down-staging intent. Overall, 47 patients received living donor LT (LDLT), and 12 patients underwent deceased donor LT (DDLT). Based on pathological examination of hepatic specimens, 13 patients had HCC beyond UCSF transplantation criteria. There were 3 cases (5%) of hospital mortality within 3 months after LT, and 15 out of the remaining 56 patients (26.8%) experienced HCC recurrence after LT. By the end of this study, 39 patients (66.1%) were still alive, and 3 of them were alive with recurrent HCC. Additionally, twelve patients (20.3%) were dead of recurrent HCC, and 5 patients (8.5%) were dead because of diseases other than HCC.

Outcomes of patients

After LT, the median follow-up period for all patients was 29.0 months, ranging from 0.4 to 149.0 months. During the follow-

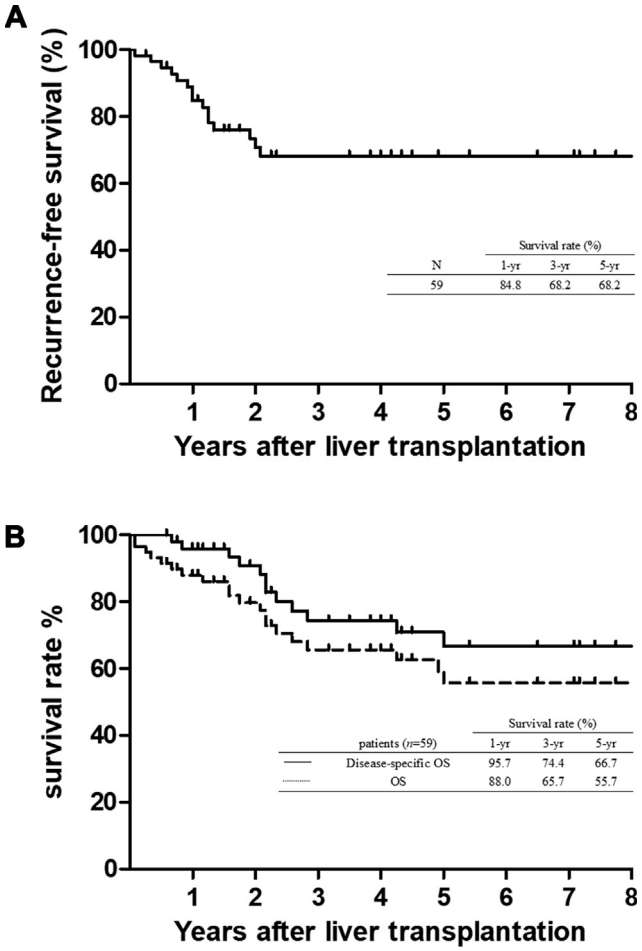

Fig. 1 **Kaplan–Meier cumulative recurrence-free survival (RFS) and overall survival (OS) curves of the patients after liver transplantation (LT) for recurrent hepatocellular carcinoma following primary liver resection**. (A) RFS curve of patients after LT. (B) The OS and disease-specific OS for patients with HCC after LT.

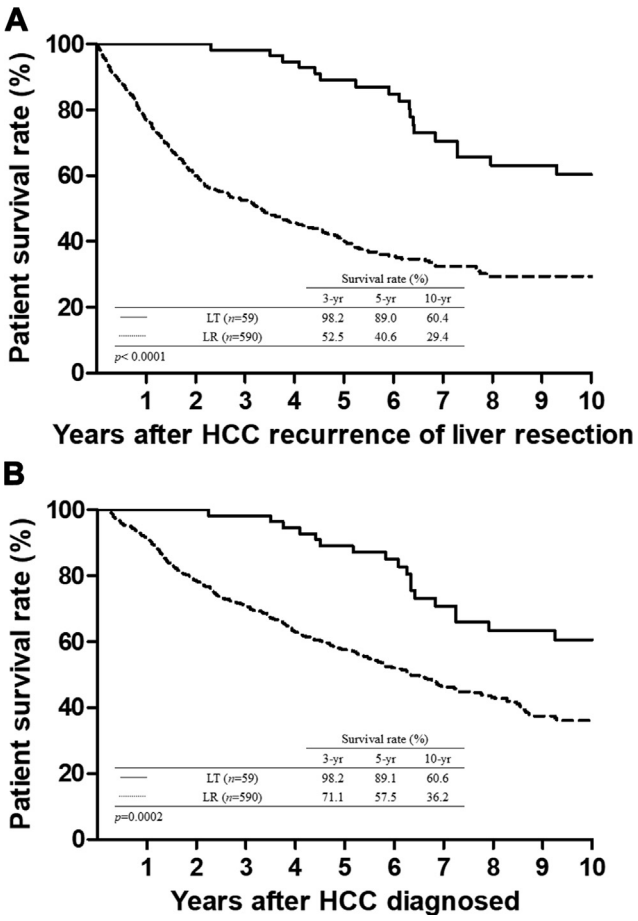

Fig. 2 **Kaplan–Meier cumulative overall survival (OS) of the patients with hepatocellular carcinoma (HCC).** (A) The OS rates calculated from the time of HCC recurrence following primary liver resection (LR) were significant better in the patients with LT than that of the patients without LT. ($p < 0.0001$) (B) The OS rates measured from the time of HCC diagnosed were significant better in the patients with LT as compared to the patients without LT. ($p = 0.0002$).

up period, the 1-, 3- and 5-year RFS rates after LT were 84.8%, 68.2% and 68.2%, respectively [Fig. 1A]. The 1-, 3- and 5-year OS rates after LT were 88.0%, 65.7% and 55.7%, respectively. However, disease-specific OS rates were 95.7%, 74.4%, and 66.7% at 1, 3 and 5 years after LT, respectively [Fig. 1B].

Moreover, patients who had undergone LT had better long-term outcomes as compared with those patients who had HCC recurrence after primary LR but not received LT. The long-term outcomes of patients were significantly prolonged in patients with LT. The 3-, 5- and 10-year OS rates calculated from the time of HCC recurrence following primary LR were 98.2%, 89.0% and 60.4%, respectively, for the patients with LT, and 52.5%, 40.6% and 29.4%, respectively, for the patients without LT [Fig. 2A, $p < 0.0001$]. The 3-, 5- and 10-year OS rates measured from the time of HCC diagnosed were 98.2%, 89.1% and 60.6%, respectively, for the patients with LT, compared to 71.1%, 57.5% and 36.2%, respectively, for the patients without LT [Fig. 2B, $p = 0.0002$].

Prognostic factors affecting outcomes after LT

The prognostic factors affecting HCC recurrence after LT were further examined from the clinicopathologic features of patients related to LR and LT, and are summarized in [Table 2]. Univariate analysis identified 7 significant factors including, maximum tumor size ≥5 cm at primary LR, extent of LR ≥ 3 segments, period between post-LR HCC recurrence and LT ≥ 1 year, tumor number >3 nodules at LT, maximum tumor size >3 cm at LT, presence of microvascular invasion at LT and beyond UCSF transplantation criteria. Furthermore, multivariate regression analysis of the aforementioned factors showed only 3 independent risk factors affecting HCC recurrence after LT. In addition to beyond UCSF transplantation criteria ($p = 0.018$, hazard ratio (HR) = 12.70), maximum tumor size ≥ 5 cm at LR ($p = 0.012$, HR = 7.90) and period between post-LR HCC recurrence and LT ≥ 1 year ($p = 0.030$, HR = 7.57) were independent prognostic factors of HCC recurrence following LT in this study.

Similarly, [Table 3] summarized univariate and multivariate analysis of prognostic factors affecting OS after LT. Although univariate analysis identified 5 significant factors, multivariate regression analysis showed HCC recurrence after LT ($p = 0.012$, HR = 5.45) was the only independent risk factor affecting OS after LT.

Patient's outcome driven by prognostic factors

The influence of each prognostic factor on the outcomes of patients, in terms of RFS, is illustrated in [Fig. 3]. Patients with HCC that met the UCSF criteria had reasonably better RFS than those beyond UCSF criteria, in which the 3-year RFS rates were 86.0% versus 13.8%, respectively [Fig. 3A, $p < 0.0001$]. The 5-year RFS rate for patients who had maximum tumor size ≥5 cm at initial LR was only 35.9% as compared with the opposite group that enjoyed a better 5-year RFS rate of 80.2% [Fig. 3B, $p = 0.006$] Most importantly, a shorter duration between post-LR HCC recurrence and LT had a better RFS curve than that of a duration beyond 1 year. The 5-year RFS rates were 87.7% versus 44.4%, respectively [Fig. 3C, $p = 0.001$].

In order to clarify the significance of waiting time, multiple cutoffs for duration between post-LR HCC recurrence and LT were further evaluated using Akaike information criterion (AIC) that lower values indicate better model fit [Table 4]. As a result, the waiting period between post-LR HCC recurrence and LT beyond 12 months was confirmed as a significant prognostic factor for HCC recurrence after salvage LT.

Discussion

Nowadays, LR is without a doubt offering potential curative therapy available to treat patients with HCC [15–17]. Nonetheless, LR for patients with HCC is mainly frustrated by the estimated less than 30% of resection rate and high incidence of postoperative recurrence that could reach almost 70% at 5 years [18–20]. Apart from that, the ratio of patients with recurrent HCC eligible for repeat LR is very low as well [21,22]. Accordingly, salvage LT has now become the most promising strategy for these patients, which not only eradicates

Table 2 Univariate and multivariate analyses of clinicopathological factors affecting HCC recurrence of patients after liver transplantation.

Factors (patient number)	Univariate analysis			Multivariate analysis	
	HR	95% CI	*p* value	HR (95% CI)	*p* value
Sex (male, female) (51 *vs.* 8)	1.04	0.24–4.54	0.951	–	–
Hepatitis B virus (positive, negative) (48 *vs.* 11)	1.23	0.31–4.88	0.764	–	–
Hepatitis C virus (positive, negative) (6 *vs.* 53)	0.78	0.13–4.74	0787	–	–
Liver resection					
Age at LR (<55, ≥55 years) (43 *vs.* 16)	1.48	0.48–4.58	0.497	–	–
Tumor number (single, multiple) (51 *vs.* 8)	2.00	0.43–9.31	0.377	–	–
Maximum tumor size (≥5, < 5 cm) (16 *vs.* 43)	5.43	1.64–18.02	0.006	7.90 (1.59–39.29)	0.012
Microvascular invasion (yes, no) (4 *vs.* 55)	2.48	0.35–17.5	0.363	–	–
Satellite nodule (yes, no) (10 *vs.* 49)	1.97	0.51–7.62	0.322	–	–
Histology grade (I/II, III/IV) (48 *vs.* 11)	1.07	0.30–3.92	0.914	–	–
Extent of LR (≥3, <3 segments) (14 *vs.* 45)	4.90	1.40–17.15	0.013	0.24 (0.04–1.51)	0.129
Recurrent time after LR (≥1, < 1 year) (42 *vs.* 17)	2.57	0.83–7.98	0.102	–	–
HCC recurrence to LT (≥1, <1 year) (26 *vs.* 33)	5.71	2.01–16.20	0.001	7.57 (1.22–47.08)	0.030
Locoregional therapy before LT (yes, no) (51 *vs.* 8)	1.83	0.42–7.82	0.419	–	–
Liver transplantation					
Age at LT (<55, ≥55 years) (33 *vs.* 28)	1.58	0.57–4.37	0.376	–	–
AFP (≥200, <200 ng/ml) (11 *vs.* 48)	1.28	0.36–4.54	0.702	–	–
MELD score (≥20, <20) (4 *vs.* 55)	0.34	0.05–2.18	0.253	–	–
Child class (A, B/C) (41 *vs.* 18)	0.65	0.21–1.97	0.443	–	–
Type of LT (DDLT, LDLT) (12 *vs.* 47)	0.91	0.27–3.12	0.883	–	–
GRWR (≥0.8%, <0.8%) (45 *vs.* 14)	2.58	0.79–8.49	0.117	–	–
Tumor number (>3, ≤3) (10 *vs.* 49)	10.15	2.53–40.72	0.001	0.19 (0.03–1.25)	0.083
Maximum tumor size (>3, ≤3 cm) (14 *vs.* 45)	9.38	2.57–34.32	<0.001	1.08 (0.22–5.39)	0.922
Histology grade (I/II, III/IV) (44 *vs.* 15)	1.76	0.57–5.42	0.323	–	–
Satellite nodule (yes, no) (3 *vs.* 56)	4.25	0.47–38.23	0.196	–	–
Microvascular invasion (yes, no) (15 *vs.* 44)	4.05	1.20–13.67	0.024	1.67 (0.44–6.30)	0.451
UCSF (beyond, within) (13 *vs.* 46)	26.81	7.15–100.50	<0.0001	12.70 (1.55–104.3)	0.018

Abbreviations: HCC: hepatocellular carcinoma; AFP: alpha-fetoprotein; LR: liver resection; LT: liver transplantation; UCSF: University of California at San Francisco; DDLT: deceased donor liver transplantation; LDLT: living donor liver transplantation; MELD: model for end-stage liver disease; HR: hazard ratio; CI: confidence interval; GRWR; graft recipient weight ratio.

intrahepatic recurrence of HCC but also cures the concurrent cirrhotic liver disease that impedes repeat LR. However, considering the severe organ shortage as well as high cost and risk of this procedure, individualised implementation of current multimodality treatment might be more efficient to prolong patient survival time. Based on this study, the study attempted to identify prognostic factors for patients undergoing LT after LR for HCC and demonstrated that patient outcome is significantly affected by the timing of LT following post-LR HCC recurrence.

The present study evaluated predictors of salvage LT strategy amongst those factors available starting from initial LR to enable an estimation of patient outcome. This was in contrast to most other previous studies where predictors of HCC recurrence after LT were merely identified based on the clinical characteristics of LT. According to our data, HCC featured by maximum tumor size ≥5 cm at initial LR and beyond UCSF transplantation criteria at LT were independent prognostic factors of HCC recurrence after LT. Importantly, maximum tumor size ≥5 cm has been previously identified as a risk factor of HCC recurrence after LR [16,23], indicating that advanced HCC would affect patient outcome not only in initial LR but also in LT for recurrent HCC afterwards.

However, the presence of microvascular invasion has been an important prognostic factor of LT for HCC in previous studies [24–26], but it was not an independent predictor for outcome in the end result of the current study. Numerous studies have reported that greater tumor burden in terms of size and number is associated with a greater chance of microvascular invasion [27,28]. Nonetheless, the present study might be limited by its small patient number and unable to explain the observation that microvascular invasion was not identified as a significant predictor. Additionally, unexplored factors may possibly play a principal role leading to HCC recurrence after LT, and a larger cohort study may be able to clarify this issue in the future.

Interestingly, the observation of inferior outcomes after LT related to the time period between post-LR HCC recurrence and LT beyond 12 months is noteworthy in this study. Similarly, a recent multicentre study showed an association between long waiting time (>18 months) and an increased risk for HCC recurrence after LT [29]. Indeed, a longer waiting period might still lead to tumor progression and possibly dropout of patients from the LT waiting list. However, the shortage of donor availability is always an unsolvable concern, especially from Asian countries where donor livers are scarce and the list of patients awaiting LT continues to grow [30]. Hence, LDLT might be an alternative strategy to increase donor availability and to shorten the timeframe of awaiting LT for HCC patients, and early transplantation for such patients should be encouraged.

Table 3 Univariate and multivariate analyses of clinicopathological factors affecting overall survival of patients after liver transplantation.

Factors (patient number)	Univariate analysis			Multivariate analysis	
	HR	95% CI	*p* value	HR (95% CI)	*p* value
Sex (male, female) (51 *vs.* 8)	0.95	0.27–3.27	0.940	–	–
Hepatitis B virus (positive, negative) (48 *vs.* 11)	0.77	0.25–2.32	0.644	–	–
Hepatitis C virus (positive, negative) (6 *vs.* 53)	1.19	0.27–5.18	0.808	–	–
Liver resection					
Maximum tumor size (≥5, < 5 cm) (16 *vs.* 43)	3.34	1.37–8.12	0.008	1.97 (0.63–6.15)	0.238
Extent of LR (≥3, <3 segments) (14 *vs.* 45)	3.11	1.28–7.55	0.012	1.36 (0.39–4.74)	0.627
Recurrent time after LR (≥1, < 1 year) (42 *vs.* 17)	0.87	0.33–2.29	0.786	–	–
HCC recurrence to LT (≥1, <1 year) (26 *vs.* 33)	1.96	0.80–4.81	0.140	–	–
Locoregional therapy before LT (yes, no) (51 *vs.* 8)	2.90	0.38–21.72	0.299	–	–
Liver transplantation					
Age at LT (<55, ≥55 years) (33 *vs.* 28)	1.10	0.45–2.67	0.819	–	–
AFP (≥200, <200 ng/ml) (11 *vs.* 48)	1.09	0.36–3.29	0.869	–	–
MELD score (≥20, <20) (4 *vs.* 55)	0.04	0.01–47.7	0.380	–	–
Child class (A, B/C) (41 *vs.* 18)	0.55	0.23–1.35	0.195	–	–
Type of LT (DDLT, LDLT) (12 *vs.* 47)	0.75	0.22–2.57	0.650	–	–
GRWR (≥0.8%, <0.8%) (45 *vs.* 14)	1.13	0.37–3.97	0.824	–	–
Tumor number (>3, ≤3) (10 *vs.* 49)	1.58	0.57–4.38	0.375	–	–
Maximum tumor size (>3, ≤3 cm) (14 *vs.* 45)	3.23	1.25–8.31	0.015	1.83 (0.52–6.45)	0.341
Histology grade (I/II, III/IV) (44 *vs.* 15)	0.75	0.30–1.90	0.551	–	–
Satellite nodule (yes, no) (3 *vs.* 56)	1.56	0.36–6.76	0.548	–	–
Microvascular invasion (yes, no) (15 *vs.* 44)	1.69	0.66–4.32	0.270	–	–
UCSF (beyond, within) (13 *vs.* 46)	2.77	1.11–6.91	0.029	0.40 (0.09–1.61)	0.199
HCC recurrence after LT (yes, no) (15 *vs.* 44)	5.84	2.29–14.85	<0.001	5.45 (1.44–20.57)	0.012

Abbreviations: HCC: hepatocellular carcinoma; AFP: alpha-fetoprotein; LR: liver resection; LT: liver transplantation; UCSF: University of California at San Francisco; DDLT: deceased donor liver transplantation; LDLT: living donor liver transplantation; MELD: model for end-stage liver disease; HR: hazard ratio; CI: confidence interval; GRWR; graft recipient weight ratio.

Currently, LT has been considered the best therapeutic option for patients who have liver cirrhosis associated with HCC but are ineligible for liver resection. However, HCC recurrence after LT remains a major concern that accounted for 10–20% of patients in most reports of primary LT. The importance of HCC recurrence after LT was also reflected by the present study, in which it was the solely independent risk factors affecting overall survival of patients. Therefore, prevention of HCC

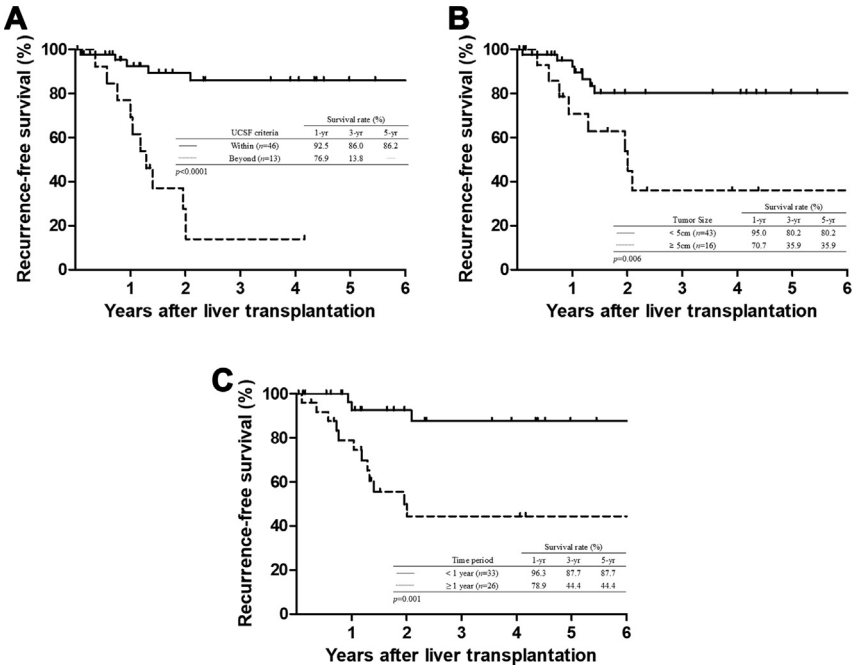

Fig. 3 **Comparison of patient outcome in terms of recurrence-free survival (RFS) on the basis of each prognostic factor.** (A) UCSF transplantation criteria. ($p < 0.0001$) (B) Maximum tumor size at the time of liver resection (LR). ($p = 0.006$) (C) The duration between post-LR HCC recurrence and the time of liver transplantation (LT). ($p = 0.001$).

Table 4 Univariate analysis of wait time from post-LR HCC recurrence to LT as predictor of HCC recurrence after LT by cox proportional hazards regression.

Wait time (months)	Univariate HR (95% CI)	*p*	AIC
≥3 *vs* <3	1.381 (0.389–4.903)	0.618	112.74
≥6 *vs* <6	1.933 (0.545–6.853)	0.308	111.83
≥12 *vs* <12	6.373 (1.792–22.660)	0.004	102.31
≥18 *vs* <18	4.162 (1.475–11.740)	0.007	105.65
≥24 *vs* <24	3.663 (1.326–10.120)	0.012	106.970

Abbreviations: LR: liver resection; HCC: hepatocellular carcinoma; LT: liver transplantation; HR: hazard ratio; CI: confidence interval; AIC: Akaike information criterion.

recurrence after LT might be an important task to improve long-term outcome of patients. However, the incidence of HCC recurrence after LT in the present study might be a little higher than the majority of reports in the literature. The theoretical explanation of this phenomenon could possibly be related to host factors, in which patients who were recurrent disease perhaps had a tendency or higher risk to develop HCC recurrence again. Moreover, many studies had similar results that a relatively higher ratio of HCC recurrence in salvage LT as compared with primary LT [10,31]. Additionally, the use of locoregional therapy could probably halt tumor progression as well as down-staging HCC in patients awaiting LT. Studies had also demonstrated that certain effect of locoregional therapy could diminish the risk of HCC recurrence after LT [32,33]. Nonetheless, locoregional therapy prior to LT had no significant benefit in terms of RFS in this study. The present study might be limited by its small patient number with a heterogeneous subgroup and unable to explain the observation. Apart from that, the majority of patients nearly 90% had locoregional therapy prior to LT leading to difficulty of statistical difference.

Additionally, the surgical difficulty in LT for patients who have undergone previous LR remains a great challenge despite the advancement of surgical instruments and techniques. In such circumstances, the difficulty might be related to adhesion above the liver's surface, vigorous portal collaterals and/or extensive hilar dissection performed during previous LR. Although some studies have shown the difficulty of salvage LT neither increases postoperative complications nor negatively affects the prognosis of patients [13,34,35], a longer operative time and possibly more blood loss during the operation would come across to surgeons. Therefore, the use of bio-resorbable membranes in primary LR might be able to reduce perihepatic adhesions and decrease the surgical difficulty of salvage LT [36].

Conclusion

In summary, surgical management including LR and LT could be the best potential curative therapy available for patients with HCC depending on suitable clinical scenario. As such, LR followed by LT for late stage liver cirrhosis and/or recurrent HCC could be a promising strategy for patients with HCC. Although the study is limited by a small number of patients and its retrospective nature, several marked observations might be helpful in the decision-making of therapeutic options for patients with HCC. The results illustrate that tumor features at both LR and LT are likely to play potential roles affecting patient outcome, indicating that large tumor size at LR should be taken into caution tending to HCC recurrence after salvage LT. Most importantly, LT should be considered as soon as possible preferably within 1 year whenever recurrent HCC following LR meets transplantation criteria.

Conflicts of interest

All authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bj.2019.04.001.

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