ORIGINAL ARTICLE

Time of Hepatocellular Carcinoma Recurrence After Liver Resection and Alpha-Fetoprotein Are Important Prognostic Factors for Salvage Liver Transplantation

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Salvage liver transplantation (LT) is considered a feasible option for the treatment of recurrent hepatocellular carcinoma (HCC). We performed this multicenter study to assess the risk factors associated with the recurrence of HCC and patient survival after salvage LT. Between January 2000 and December 2011, 101 patients who had previously undergone liver resection (LR) for HCC underwent LT at 3 transplant centers in Korea. Sixty-nine patients' data were retrospectively reviewed for the analysis. The recurrence of HCC was diagnosed at a median of 10.6 months after the initial LR, and patients underwent salvage LT. Recurrences were within the Milan criteria in 48 cases and were outside the Milan criteria in 21 cases. After salvage LT, 31 patients had HCC recurrence during a median follow-up period of 24.5 months. There were 24 deaths, and 20 were due to HCC recurrence. The 5-year overall survival rate was approximately 54.6%, and the 5-year recurrence-free survival rate was 49.3%. HCC recurrence within the 8 months after LR [hazard ratio (HR) = 3.124, $P = 0.009$], an alpha-fetoprotein level higher than 200 ng/mL (HR = 2.609, $P = 0.02$), and HCC outside the Milan criteria at salvage LT (HR = 2.219, $P = 0.03$) were independent risk factors for poor recurrence-free survival after salvage LT. In conclusion, the timing and extent of HCC recurrence after primary LR both play significant roles in the outcome of salvage LT. ***Liver Transpl 20:1057-1063, 2014***. **© 2014 AASLD.**

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For patients presenting with early-stage hepatocellular carcinoma (HCC) and preserved liver function, the optimal initial treatment is still a matter of debate. Advocates of primary liver transplantation (LT) for these patients emphasize that LT is the most definitive treatment option for HCC and that LT can be performed with relatively low operative risk to the recipient in such cases.[1,2] However, the organ shortage is undoubtedly a major obstacle whenever the clinician opts for LT. Liver resection (LR) for early HCC can be applied whenever the surgeon chooses to do so, and in experienced hands, it can be done with very low morbidity and mortality.[3-5] Although LR can be criticized for its high recurrence rate, these

Additional Supporting Information may be found in the online version of this article.

Abbreviations: AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; HR, hazard ratio; LR, liver resection; LT, liver transplantation.

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patients may still be candidates for salvage LT when HCC recurs. This strategy of initial LR followed by salvage LT in the case of HCC recurrence is becoming more widely accepted in centers around the world.[6-8]

Our group previously reported 17 cases of salvage living donor LT performed at our center and suggested that the pathological characteristics of their HCCs (eg, the presence of microvascular invasion) profoundly affected the outcomes of these patients.[9] Following up our previous study, we expanded the patient population to include salvage LT recipients from 3 high-volume transplant centers in Korea, and we analyzed the factors associated with the recurrence of HCC in recipients of salvage LT. In this multicenter study, we aimed to create selection criteria for the patients who are most likely to benefit from salvage LT.

PATIENTS AND METHODS

Study Population

From January 2000 to December 2011, 101 patients with a previous history of LR for HCC underwent LT at Samsung Medical Center (Seoul, Korea), Ajou University Medical Center (Suwon, Korea), and Seoul National University Hospital (Seoul, Korea). The medical records of these patients were retrospectively reviewed. Adult patients undergoing LT for the first time with pathologically proven HCC were included in the analysis. Staging was performed according to the 7th edition of the American Joint Committee on Cancer tumor-node-metastasis staging system.[10]

Nineteen of the 101 patients underwent transplantation for reasons other than HCC recurrence after LR (liver failure after LR or progression of cirrhosis), and they were excluded from the analysis. One patient was excluded after a review of medical records revealed cholangiocarcinoma as the pathological diagnosis at LT. Precise pathological data were not obtainable for 12 patients because their LRs were performed at outside hospitals and they were referred to 1 of the 3 centers for LT. After the exclusion of these 32 patients, 69 patients were included in the analysis. The patient selection process is outlined in Fig. 1. This study was approved by the institutional review boards of the participating centers.

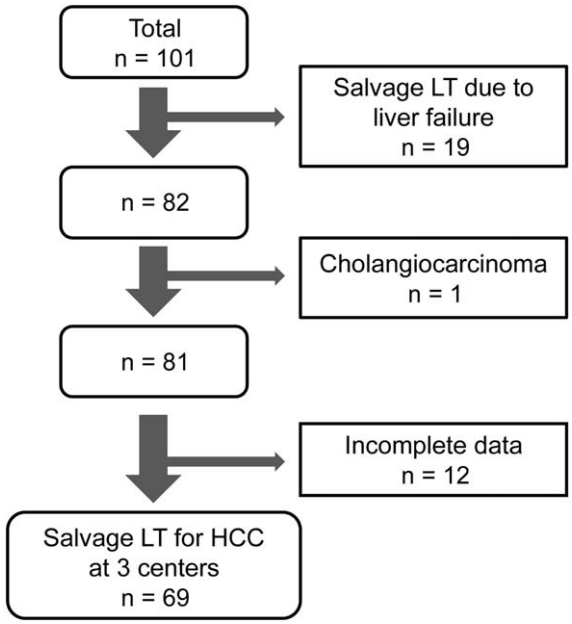

Figure 1. Outline of the patient selection process.

Surveillance and Treatment After the Initial LR

HCC management was uniformly performed at the 3 centers according to clinical practice guidelines for HCC put forward by the Korean Liver Cancer Study Group and the National Cancer Center.[11] LR was considered for resectable HCC in patients with adequate liver function and sufficient expected liver reserve after LR. Because the overall surgical mortality rate was very low, LR was considered an option even for intermediate-stage HCC according to the surgeon's discretion. Liver reserve was estimated via the measurement of the residual blood concentration of indocyanine green 15 minutes after the intravenous injection of the dye. Anatomic LR was considered first, but when the estimated liver reserve was insufficient for major resection, nonanatomic tumorectomy with at least a 1-cm safety margin was performed. Follow-up after LR consisted of liver function tests, alpha-fetoprotein (AFP) levels, protein induced by vitamin K absence or antagonist II levels, and a radiological evaluation of the liver (including ultrasonography, liver 3-phase computed tomography scanning, or liver magnetic resonance imaging every 3 months during the first year and every 6 months from the second year on). Oral nucleos(t)ide analogues were given to patients with hepatitis B, and chronic hepatitis C treatment was given to select patients.

The appearance of a new lesion in the liver with typical radiological features of HCC was considered to indicate HCC recurrence. Upon the detection of recurrence, chest computed tomography or positron emission tomography/computed tomography was performed to rule out the existence of distant metastases. Patients with recurrent HCC without evidence of extensive local disease (macroscopic vascular invasion) or distant metastases were considered for salvage LT. We did not strictly adhere to the Milan criteria when we were selecting patients for living donor LT, and approximately 30% of the patients in our study population underwent transplantation for recurrent HCC beyond the Milan criteria. Patients on the waiting list or patients who initially refused LT were treated with locoregional therapies, including transarterial chemoembolization, radiofrequency ablation, and radiotherapy, whenever possible.

Follow-Up After Salvage LT

Basiliximab was given as induction immunosuppression, and a standard 3-drug regimen consisting of a calcineurin inhibitor (tacrolimus or cyclosporine), mycophenolic acid (mycophenolate mofetil), and

TABLE 1. Clinicopathological Characteristics of the Patients at the Initial LR (n = 69)

Age (years)*	50.5 ± 9.3
Sex (n)	
Male	62
Female	7
Child-Pugh class at LR (n)	
A	63
B	6
Underlying liver disease (n)	
Hepatitis B virus	66
Hepatitis C virus	3
Median preoperative AFP at LR (ng/mL)	114.5
Type of LR (n)	
Major resection	18
Minor resection	51
Tumor size (cm)*	4.1 ± 2.6
Tumor number (n)	
1	49
Multiple	20
Milan criteria at LR (n)	
Within	50
Beyond	19
Microvascular invasion (n)	
Yes	31
No	38

*The data are presented as means and standard deviations.

TABLE 2. Clinicopathological Characteristics of the Patients at Salvage LT (n = 69)

Time to HCC recurrence after LT (months)*	10.6 (2-137)
Pre-LT locoregional treatment (n)	
Yes	64
No	5
Median preoperative AFP at LT (ng/mL)	56.0
HCC status at LT (n)	
Within Milan criteria	48
Outside Milan criteria	21
Donor type (n)	
Living donor	63
Deceased donor	6
Follow-up after LT (months)*	24.5 (1-189)
HCC recurrence after salvage LT (n)	
Yes	31
No	38
Patient outcome after salvage LT (n)	
Survival	45
Death	24

*The data are presented as medians and ranges.

corticosteroids was used as maintenance immunosuppression. Hepatitis B virus prophylaxis, including intravenous hepatitis B immunoglobulin and an oral nucleos(t)ide analogue, was given to patients undergoing transplantation for hepatitis B virus–related disease.

Surveillance for HCC recurrence after salvage LT was identical to the surveillance after the initial LR. Recurrent HCC after salvage LT was treated in a case-by-case manner with various combinations of radiofrequency ablation, transarterial chemoembolization, and radiotherapy. Upon the diagnosis of recurrence, the level of immunosuppression was lowered, and in select cases, the calcineurin inhibitor was switched to sirolimus. Sorafenib was added for patients with distant metastases of HCC.

Statistical Analysis

Survival was calculated with the Kaplan-Meier method, and survival curves were compared with log-rank tests. Cutoff points for predictors of survival (early recurrence of HCC after LR and high serum AFP levels at LR) were calculated via the plotting of receiver operating characteristic curves and the selection of the points representing the highest sensitivity and specificity values (data not shown). Univariate and multivariate modeling was performed with Cox regression to create a model of prediction of HCC recurrence–free survival. All predictors that were significant in the univariate analysis were entered into the multivariate logistic models. A P value less than 0.05 was considered statistically significant.

RESULTS

Patient Demographics

The mean age of the patients at the time of the initial LR was 50.5 years. The study population was predominantly male (n = 62 or 89.9%). The median AFP level was 114.5 ng/mL before the initial LR. Sixty-three patients were Child-Pugh class A, and 6 patients were class B. Major LRs were performed for 18 cases, and minor LRs were performed for 51 cases. The mean tumor size was 4.1 cm, and 49 patients had single HCCs. Microscopic vascular invasion was present in 31 cases, and 50 patients were within the Milan criteria at the time of LR (Table 1).

The recurrence of HCC was diagnosed at a median of 10.6 months after the initial LR, and patients underwent salvage LT. Recurrences were within the Milan criteria in 48 cases and were outside the Milan criteria in 21 cases (Table 2).

Patient Outcomes After Salvage LT

The median hospital stay after salvage LT was 41.0 days (range = 16-104 days). Eleven patients underwent reoperation for various postoperative complications during that time. Complications requiring reoperation in these patients included bleeding (7 cases), bowel perforation (2 cases) and biliary complications (2 cases).

TABLE 3. Univariate and Multivariate Analyses of Risk Factors for HCC Recurrence After Salvage LT

	Univariate Analysis		Multivariate Analysis		
	HR	*P* Value	HR	95% Confidence Interval	*P* Value
At LR					
Pre-LR AFP (ng/mL)	1.000	0.71	—	—	—
Major hepatic resection (versus minor resection)	0.587	0.14	—	—	—
Tumor size (cm)	1.166	0.01	—	—	—
Advanced Edmondson grade	2.080	0.32	—	—	—
Microvascular invasion present	2.472	0.02	1.654	0.693-3.946	0.26
HCC beyond Milan criteria (versus within Milan criteria)	2.580	0.01	1.379	0.549-3.461	0.49
HCC recurrence within 8 months after LR (versus beyond 8 months)	5.205	<0.001	3.124	1.323-7.379	0.009
At LT					
LT center	1.115	0.79	—	—	—
Interval from HCC recurrence to LT (months)	0.988	0.27	—	—	—
AFP > 200 ng/mL at LT	4.473	<0.001	2.609	1.189-5.725	0.02
Recurrence outside Milan criteria (versus within Milan criteria)	2.620	0.008	2.219	1.073-4.589	0.03
Advanced Edmondson grade	1.892	0.23	—	—	—
Microvascular invasion present	10.094	<0.001	—	—	—

NOTE: Microvascular invasion at LT was not included in the multivariate analysis.

The median follow-up time after salvage LT was 24.5 months (range = 1-189 months). Thirty-one patients (31/69 or 44.9%) had HCC recurrence at a median of 5.4 months after LT (range = 1-47 months). There were 24 deaths after salvage LT, and 20 were due to HCC recurrence. Other causes of deaths included sepsis (n = 2) and graft failure (n = 2). The 5-year overall survival rate was 54.6%, and the 5-year recurrence-free survival rate was 49.3%.

Risk Factors for the Recurrence of HCC After Salvage LT

Clinical and pathological factors associated with the recurrence of HCC after salvage LT were analyzed. In the univariate analysis, a large tumor size, HCC advanced beyond the Milan criteria at the initial LR, the presence of microvascular invasion in the HCC at the initial LR, and HCC recurrence within 8 months of the initial LR were significant risk factors associated with recurrence after salvage LT. Also, an AFP level higher than 200 ng/mL at the time of LT, HCC beyond the Milan criteria at LT, a higher T stage at LT, and the presence of microvascular invasion in the HCC at LT were significant risk factors associated with increased recurrence after salvage LT. However, when significant factors were applied to the multivariate analysis, HCC recurrence within the 8 months after LR [hazard ratio (HR) = 3.124, $P = 0.009$], an AFP level higher than 200 ng/mL (HR = 2.609, $P = 0.02$), and HCC outside the Milan criteria at salvage LT (HR = 2.219, $P = 0.03$) were significantly associated with poor recurrence-free survival for recipients after salvage LT (Table 3).

Figure 2 shows Kaplan-Meier survival curves of recurrence-free survival after salvage LT according to the presence or absence of each risk factor found to be significant in the multivariate analysis. Clear distinctions exist between the survival curves of patients with early HCC recurrence after LR (within 8 months) and patients with late HCC recurrence after LR (beyond 8 months; $P < 0.001$), patients with high serum AFP levels at salvage LT (>200 ng/mL) and patients with low serum AFP levels at salvage LT (≤200 ng/mL; $P < 0.001$), and patients with HCC within the Milan criteria at LT and patients with HCC beyond the Milan criteria at LT ($P = 0.006$). When the number of risk factors was considered, patients with 1 or 2 risk factors had significantly poorer recurrence-free survival in comparison with patients with no risk factors. Also, patients with all 3 risk factors had significantly poorer recurrence-free survival in comparison with patients with 1 or 2 risk factors ($P < 0.001$; Fig. 3A). Overall survival did not differ among the patients with 1, 2, or 3 risk factors. However, these patients showed significantly worse survival after salvage LT in comparison with patients with no risk factors ($P < 0.001$; Fig. 3B).

DISCUSSION

The principal finding of this study is that the prognosis of patients after salvage LT is affected not only by the Milan criteria status at the time of LT but also by factors pertaining to the biological behavior of the recurrent HCC after the initial LR. We identified 3 independent risk factors affecting HCC recurrence after salvage LT: the interval between the initial LR

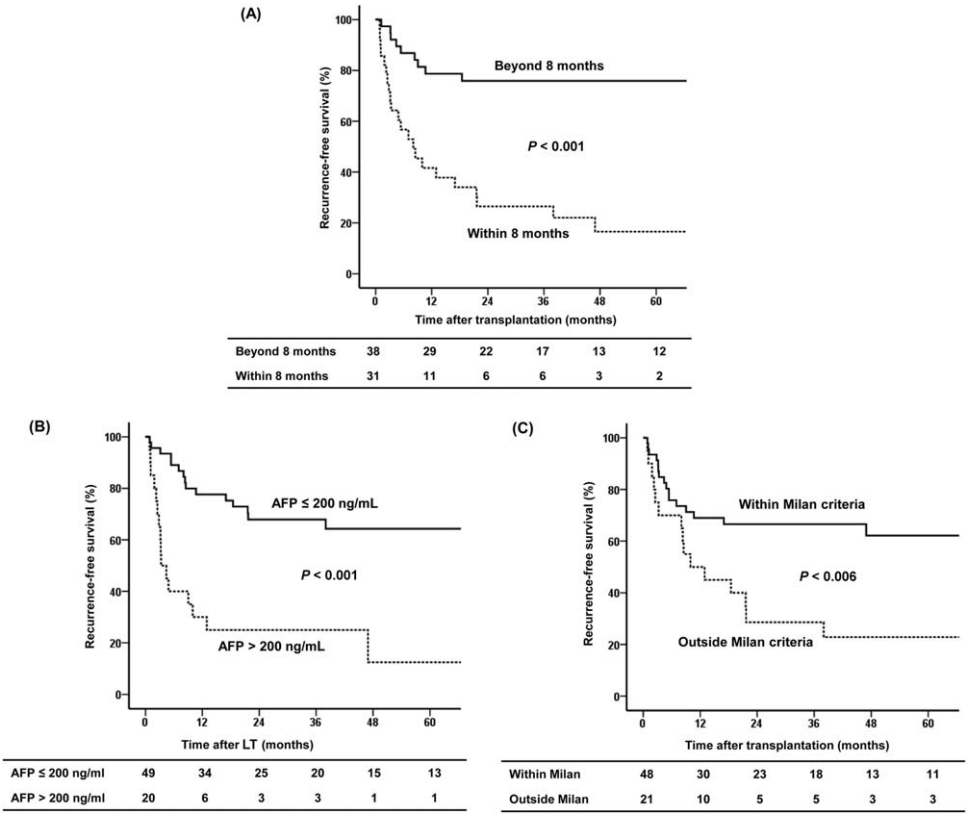

Figure 2. Survival curves showing differences in recurrence-free survival according to the 3 risk factors: (A) early recurrence of HCC after the initial LR, (B) elevated AFP level at salvage LT, and (C) HCC beyond the Milan criteria at salvage LT.

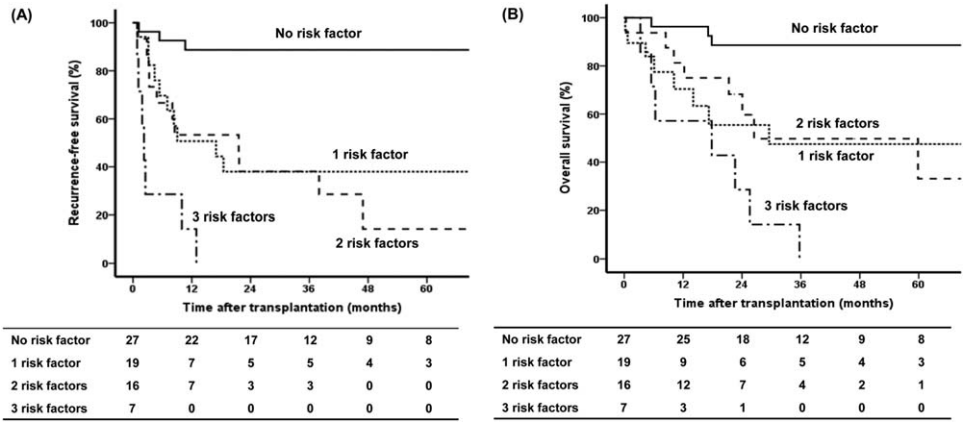

Figure 3. Survival analyses of patients after salvage LT according to the number of risk factors. (A) Recurrence-free survival was significantly decreased with an increasing number of risk factors ($P < 0.001$) except between the subgroups with 1 and 2 risk factors (not significant). (B) Overall survival did not differ between subgroups with 1, 2, or 3 risk factors; however, the survival for all these subgroups was significantly decreased in comparison with the survival for the subgroup with no risk factors ($P < 0.001$).

and HCC recurrence, the AFP level at the time of salvage LT, and the Milan criteria status at LT. The presence of 1 or more of these risk factors was associated with significantly low overall and recurrence-free survival for salvage LT recipients. Therefore, we recommend that these risk factors as well as the Milan criteria be carefully considered when a patient is being selected for salvage LT. When any of the risk factors are present, the patient may have a poor prognosis with an increased risk of HCC recurrence after salvage LT, regardless of the Milan criteria.

Recent data support the view that there is no difference in survival between primary LT and secondary (salvage) LT.[6,9,12] Accordingly, many centers have adopted the strategy of initial LR followed by salvage LT for detected HCC recurrence as the established

practice for the primary surgical treatment of early-stage HCC within the Milan criteria.[6-8] However, this approach is not without important points warranting concern. One possible problem is the fact that selection criteria for salvage LT have not been well established. The Milan criteria, which are the most widely accepted guidelines for the selection of LT candidates with underlying HCC, do not include patients undergoing LT for recurrent HCC after the initial LR.[13] However, the Milan criteria are applied to salvage LT candidates in clinical practice, and they have never been questioned or challenged. Another important point of concern is that some patients may have recurrent HCC after the initial LR that is beyond the Milan criteria and thus may be deprived of a chance for a definitive cure by LT, which may otherwise have been possible had the patient undergone LT as the initial treatment. A study by Fuks et al.[14] showed that with a strategy of LR followed by salvage LT, nearly half of the patients with HCC recurrence did not undergo transplantation: for one-third of the cases, this was due to recurrence beyond the Milan criteria.

In our series, in addition to the Milan criteria, the early recurrence of HCC after the initial LR and high serum AFP levels before salvage LT significantly affected recurrence-free survival after salvage LT. A fourth variable, the presence of microvascular invasion in the explant liver, was a strong risk factor for HCC recurrence after salvage LT in the univariate analysis. However, we did not include this in the multivariate analysis because it is not clinically relevant to predict post-LT survival at a time point before salvage LT with a variable that becomes evident only after transplantation. The findings are in accordance with previous reports on the outcomes of repeat hepatectomy and other treatment modalities for HCC recurrence after curative LR. A poor prognosis was seen for patients undergoing repeat hepatectomy for HCC recurrence after curative LR when there was portal vein invasion at the first or second resection, there were multiple HCCs at the primary hepatectomy, and there was a disease-free interval of 1 year or less after the primary hepatectomy.[15-17] These early recurrences were believed to be intrahepatic metastases from the primary HCC and thus reflected the lower survival rate of patients who developed intrahepatic metastases. Fuks et al.[14] also pointed out 5 risk factors related to the likelihood of HCC recurrence beyond the Milan criteria after LR for early transplantable HCC. These factors are microvascular invasion, the presence of satellite nodules, a tumor size >3 cm, a poorly differentiated tumor, and cirrhosis, which collectively reflect the characteristics of the HCC and the background liver. The authors stated that the strength of the salvage transplantation strategy is the possibility of acquiring a large specimen of the tumor as well as the background liver for a detailed analysis and possibly predicting the likelihood of HCC recurrence beyond the Milan criteria in these patients and thus precluding the possibility of salvage LT. In our study, we have focused on the outcome after salvage LT, which is different from the endpoints of the previous study; it is interesting to see that there is a lack of significance for primary HCC characteristics such as the tumor size and microvascular invasion. It would be interesting to see what the outcome would be if a subgroup of patients with unfavorable tumor characteristics diagnosed after the initial LR preemptively underwent transplantation. Among the 16 patients excluded from this analysis who underwent salvage LT before the recurrence of HCC (for post-LR liver failure or progressive cirrhosis), 4 patients had 3 or more of the risk factors identified by Fuks et al. Two patients were alive without HCC recurrence 83 and 111 months after salvage LT. One patient had immediate recurrence and died of a subarachnoid hemorrhage 3 months after salvage LT. One patient died 14 months after salvage LT because of fungal pneumonia. No evidence of HCC recurrence was found in this patient until the time of death.

This is a multicenter study involving a considerable number of cases of salvage LT, and it is the first study to suggest a guideline for selecting patients for salvage LT. However, the analysis has several limitations. The first is related to its multicenter nature, with the possibility of wide variations in treatment choices and postoperative care. Although the 3 centers participating in this study have been following the clinical practice guidelines for HCC put forward by the Korean Liver Cancer Study Group and the National Cancer Center, complete uniformity in the management of HCC patients could not be guaranteed. The second is its retrospective design with a relatively short post-transplant follow-up of 24.5 months. The probability of various biases is inherent to a retrospective analysis such as this, and a median period of 24.5 months after LT may not be sufficiently long enough to capture all cases of post-LT HCC recurrence. Third, the study includes LR for cases with intermediate-stage HCC and salvage LT for HCC beyond the Milan criteria. Also, the large number of cases with HCCs beyond the Milan criteria at salvage LT may have had an exaggerating effect on the significance of this variable as a prognostic factor. These are not common practices at all transplant centers, and this may hinder our findings from being applicable to all programs. However, nearly 80% of our cases (55/69) were Barcelona Clinic Liver Cancer stage 0 or A at the time of LR. Also, as described earlier, all cases were selected for LR according to the standards of local practice guidelines, although the criteria were expanded in comparison with Western standards.

In conclusion, we have shown that the recurrence of HCC within the 8 months after the initial LR, a high serum AFP level (>200 ng/mL), and HCC beyond the Milan criteria at LT are unfavorable risk factors after salvage LT. Patients with none of the risk factors showed a 5-year survival rate of 88.6%. The Milan criteria alone did not provide an optimal guideline for salvage LT: the disease-free interval after the initial LR and the pre-LT AFP level should also be considered when a patient is being selected for salvage LT.

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