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ORIGINAL ARTICLE

Outcomes of Salvage Liver Transplantation and Re-resection/Radiofrequency Ablation for Intrahepatic Recurrent Hepatocellular Carcinoma: A New Surgical Strategy Based on Recurrence Pattern

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Abstract

Background The treatment of intrahepatic recurrent hepatocellular carcinoma (HCC) has been poorly investigated, and the optimal treatment strategy remains unclear.

Aims The aim of this study was to compare outcomes between salvage liver transplantation (SLT) and re-resection (RR)/radiofrequency ablation (RFA) for intrahepatic recurrent HCC according to recurrence pattern.

Methods Based on postoperative histopathological examination, 122 patients with intrahepatic recurrent HCC were divided into an intrahepatic metastasis (IM, $n = 75$) group and a multicentric occurrence (MO, $n = 47$) group. The demographic, clinical, and primary and recurrent tumor characteristics of the IM group and the MO group were collected and compared. Overall survival (OS) and disease-free survival (DFS) were analyzed, and subgroup analysis according to retreatment type (SLT vs. RR/RFA) was conducted. Twenty-nine clinicopathological variables potentially related to prognostic factors affecting survival were analyzed using a Cox proportional hazard model.

Results The patients that received SLT treatment exhibited favorable DFS compared to patients that received RR/RFA ($P = 0.002$). OS ($P < 0.001$) and DFS ($P = 0.008$) rates were significantly increased in the MO group compared with in the IM group. Subgroup analysis revealed that DFS was significantly improved for patients in the MO group treated with SLT compared to patients treated with RR/RFA ($P = 0.017$). Recurrence pattern was an independent prognostic factor for both OS [hazard ratio (HR) = 0.093, 95% confidence interval (CI): 0.026–0.337, $P < 0.001$] and DFS (HR = 0.318, 95% CI: 0.125–0.810, $P = 0.016$; HR = 3.334, 95% CI: 1.546–7.18, $P = 0.002$).

Conclusions For patients with intrahepatic recurrent HCC, an MO recurrence pattern is associated with better long-term outcomes than the IM pattern. SLT is the preferred option for intrahepatic recurrent HCC, especially for MO cases.

Keywords Intrahepatic recurrence · Intrahepatic metastasis · Multicentric occurrence · Salvage liver transplantation · Re-resection · Radiofrequency ablation

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the second most frequent cause of cancer death worldwide [1]. Hepatic resection remains a first-line treatment for patients with small HCC and preserved liver function. However, a high recurrence rate, which exceeds 70% 5 years after resection [2–4], is a major complication after curative resection and leads to poor long-term survival. Intrahepatic recurrence accounts for 80% of recurrences [5]. Therefore, optimal management strategies for intrahepatic recurrent HCC would improve long-term patient outcomes.

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Intrahepatic recurrent HCC in the remnant liver originates from either intrahepatic metastasis (IM) from the primary resected tumor or from multicentric occurrence (MO) [6–8]. IM is believed to arise from tumor cell that spread through the portal venous system, whereas MO derives from "de novo carcinogenesis" under cirrhotic conditions.

Curative treatments for intrahepatic recurrent HCC are similar to primary tumor treatments and include repeat resection (RR), radiofrequency ablation (RFA), and salvage liver transplantation (SLT).The treatment effects differ significantly between IM and MO. Several studies have recommended that patients with MO can undergo RR or RFA to improve long-term survival, while patients with IM have significantly reduced long-term survival [9–11]. SLT has been proposed to be the optimal option, representing the best theoretical solution to eliminate both the tumor and the underlying hepatic disease [12–14]. Unfortunately, no data are available to compare the outcomes of SLT and RR/RFA between IM and MO cases.

Therefore, we investigated the outcomes of SLT and RR/RFA according to recurrence patterns (IM and MO) in patients suffering intrahepatic recurrent HCC.

Methods

Patients

Between February 2007 and June 2016, 756 consecutive HCC patients fulfilling the Milan criteria (a solitary tumor $\leq$ 5 cm in diameter or $\leq$ 3 nodules of $\leq$ 3 cm in diameter) underwent curative resection at the Department of Liver Surgery and Liver Transplantation Center of West China Hospital, Sichuan University, and received follow-up care. Curative resection was defined as complete excision of the tumor with clear microscopic margins and no evidence of residual tumors by ultrasound, computed tomography, or angiography 1 month after surgery. A total of 296 patients experienced recurrent HCC, including 267 patients with intrahepatic recurrence. Of these 267 patients, 122 patients received a histopathological examination (36 underwent SLT, 74 underwent RR, and 12 underwent RFA). Another 29 patients with extrahepatic HCC and 145 patients who did not receive a histopathological examination were excluded from the study (Fig. 1).

Determination of Intrahepatic Recurrence Type

IM and MO were defined as described previously [15–18].

Pathological diagnostic criteria for IM: recurrent tumors consisting of moderately or poorly differentiated HCC with the same or a lower degree of differentiation than the primary tumor.

Pathological diagnostic criteria for MO:

(1) Recurrent tumors consisting of well-differentiated HCC occurring in a different hepatic segment, even with a history of moderately or poorly differentiated HCC.
(2) Both primary and recurrent tumors are well-differentiated HCCs.
(3) Recurrent tumor containing peripheral regions of adenomatous hyperplasia.
(4) Recurrent cancer with higher levels of pathological differentiation.

Patients were divided into two groups based on recurrence pattern: the IM group ($n = 75$) and the MO group ($n = 47$). Demographic, clinical, and primary and recurrent tumor characteristics for the IM and MO groups were collected and compared. OS (OS) and disease-free survival (DFS) were analyzed, and subgroup analysis according to treatment (SLT vs. RR/RFA) was performed. Twenty-nine clinicopathological variables potentially related to prognostic survival factors were analyzed using a Cox proportional hazard model.

Surgical Techniques

As described previously [19], RR and RFA were the main first-line treatment strategies for recurrent HCC. Determination of the feasibility of resection and RFA was based on the number and location of the recurrent tumors, liver function, remnant liver volume, and the general status of the patient. Patients with poor liver function, insufficient remnant liver volume, severe cirrhosis, or portal hypertension were selected for SLT.

The details of our surgical techniques and the patient selection criteria for RR and RFA have been reported previously and are nearly identical to those of the initial surgery for primary HCC [19, 20]. All of the patients received follow-up monitoring 1 month after the operation, every 3 months thereafter during the first 3 years, and every 6 months in subsequent years.

The selection criteria for the donor and recipient and the surgical techniques for both the donor and recipient operations have been described previously [21–23]. Living and deceased donations were voluntary and altruistic in all cases, and written informed consent was obtained from both donors and recipients before surgery. Maintenance immunosuppression consisted of a triple-drug regimen that included tacrolimus or cyclosporine, mycophenolate, and prednisone. An oral nucleoside analogue combined with individualized low-dose intramuscular hepatitis B immunoglobulin was given as monoprophylaxis for patients with a chronic hepatitis B

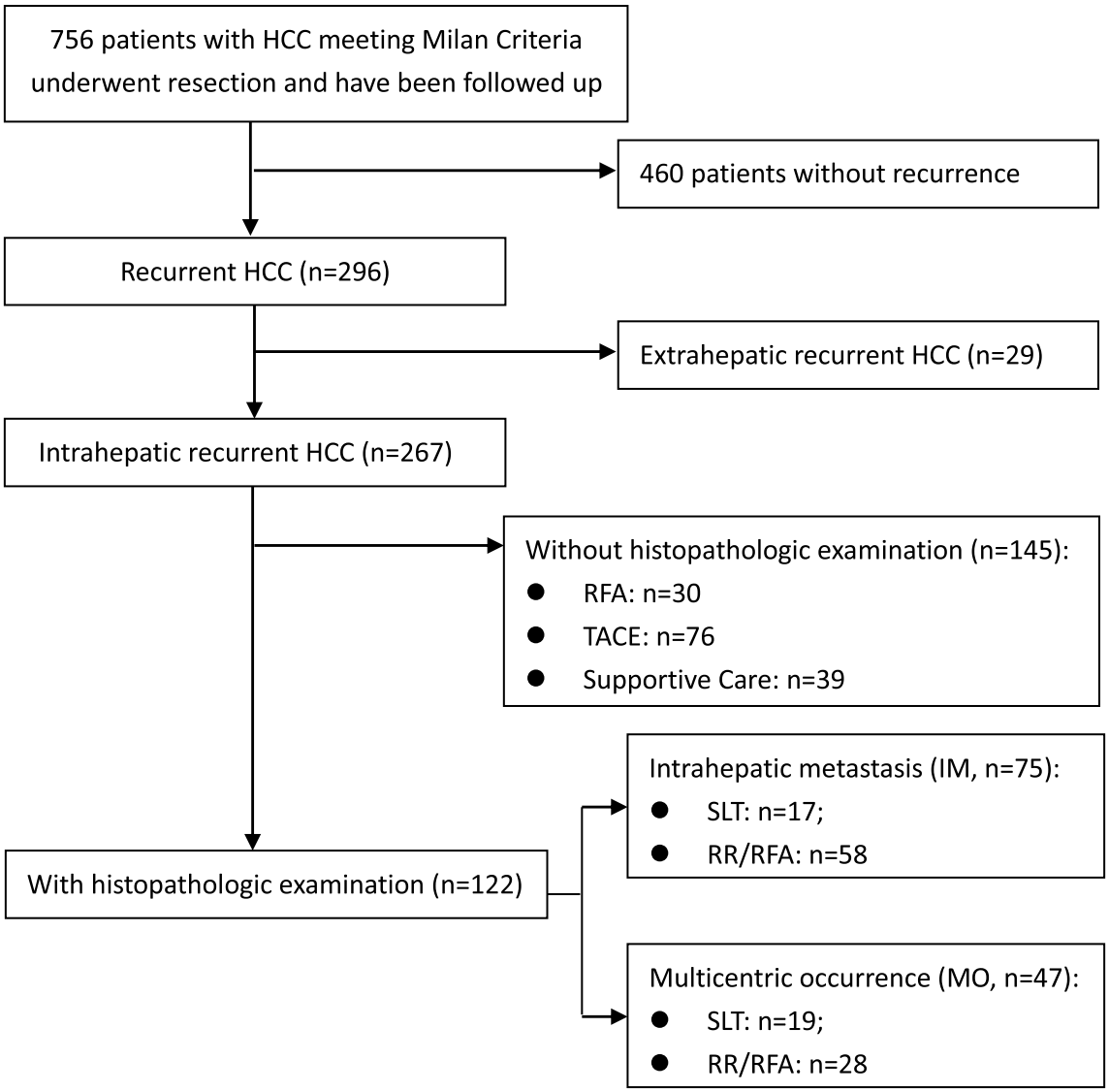

Fig. 1 Flow schematic of patients' retreatment. *HCC* hepatocellular carcinoma, *SLT* salvage liver transplantation, *RR* re-resection, *RFA* radiofrequency ablation, *TACE* transarterial chemoembolization

virus (HBV) infection. Surveillance for HBV recurrence was performed via monitoring of liver biochemistry and hepatitis B surface antigen (HBsAg), hepatitis B e antigen, and hepatitis B virus-deoxyribose nucleic acid (HBV-DNA) levels initially at each follow-up at monthly intervals after liver transplantation and at 3-month intervals thereafter.

The study was approved by the Ethics Committee of West China Hospital, Sichuan University. Written informed consent for patient information to be stored in the hospital's prospectively maintained database and to be used for research was obtained from all patients.

Follow-Up Visits

All of the enrolled patients received regular follow-up monitoring until death or termination of the study. Physical examination, blood cell and differential counts, liver function tests, alpha-fetoprotein (AFP) levels, HBV marker and HBV-DNA levels, and imaging examinations were included in the follow-up evaluations as necessary. Tumor recurrence was diagnosed based on the identification of a new lesion in at least two radiological examinations and increased AFP levels. The time to recurrence is defined as the time from resection until radiological detection of a recurrent tumor. The last follow-up date was at the end of December 2016 unless the patient died before

that time. The overall median follow-up duration was 51.14 ± 27.62 months (8–119 months).

Statistical Analysis

Continuous variables are expressed as the mean ± standard deviation and were compared between the groups using the *t* test or the Mann–Whitney *U* test for variables with an abnormal distribution. Categorical data were compared using the χ^2 test or Fisher's exact test. The OS rates were analyzed using the Kaplan–Meier method, and differences were analyzed using the log-rank test. The Cox proportional hazard model was used for univariate and multivariate analyses of prognostic factors after surgery. Two-tailed *P* values ≤ 0.05 were considered statistically significant. Calculations were performed using the SPSS package (SPSS, Inc., Chicago, IL).

Results

Clinicopathological Patient Characteristics

Of the 122 patients who received histopathological examinations, 105 were men and 17 were women, with a mean age of 48.93 ± 10.86 years (range, 25–74 years). At the recurrent stage (Table 1), 98 patients (80.3%) fulfilled the Milan criteria (solitary tumor ≤ 5 cm in diameter or ≤ 3 nodules of ≤ 3 cm in diameter).

Comparison of Clinical Parameters According to Recurrence Pattern

Between the IM group and the MO group, no significant differences were observed in age; gender; HBsAg, HBV-DNA, and AFP levels; liver function; creatinine; prothrombin time; model for end-stage liver disease (MELD) scores; white blood cell count; platelets; tumor number; tumor diameter; Milan criteria (within vs. beyond); mean intraoperative bleeding; transfusion; hospital stay; the mean time to recurrence from retreatment; or the mean follow-up time from recurrence. Significant differences were observed between the two groups for alanineaminotransferase levels (ALT: 42.36 ± 22.75 vs. 64.22 ± 67.05, $P = 0.015$), microvascular invasion (MVI, 27/75 vs. 5/47, $P = 0.002$), and type of retreatment (SLT vs. RR/RFA, $P = 0.036$).

Initially, no significant differences were observed between the IM and MO groups for resection type (Major/Minor), mean intraoperative bleeding, transfusion, hospital stay, tumor number, tumor diameter, MVI, or cirrhosis. However, the mean time to recurrence from initial resection (13.59 ± 14.74 vs. 32.26 ± 22.98, $P < 0.001$) and the mean follow-up time from initial resection (41.41 ± 24.18 vs. 66.66 ± 25.79, $P < 0.001$) were significantly longer in the MO group compared to that in the IM group (Table 2).

Comparison of Clinical Parameters According to Retreatment Type for IM and MO Respectively

Baseline characteristics by retreatment type at the time of tumor recurrence for IM and MO are summarized, respectively, in Supplementary Tables 1 and 2. The baseline characteristics were not significantly different between the two treatment groups except for AFP level ($P = 0.030$, $P < 0.001$), WBC count ($P = 0.021$, $P = 0.014$), mean intraoperative bleeding ($P < 0.001$, $P < 0.001$), transfusion ($P < 0.001$, $P = 0.003$), hospital stay ($P < 0.001$, $P < 0.001$). The total incidence of serious complications (Clavien–Dindo classification greater than grade III) was comparable between SLT and RR/RFA (6/30 vs. 7/79, $P = 0.201$, data not shown).

The clinical data regarding primary treatment and tumor characteristics for IM and MO at the initial stage were also similar between SLT and RR/RFA (Supplementary Tables 3 and 4).

DFS and OS by Retreatment Type

Longer DFS after retreatment was observed in patients that received SLT compared to those of the patients who received RR/RFA, with 1-, 3-, and 5-year DFS rates of 91.1, 70.3, and 70.3% and 64.3, 43.1, and 33.9%, respectively ($P = 0.002$, Fig. 2a). However, the corresponding 1-, 3-, 5- and 7-year OS rates after retreatment between patients that received SLT and those that received RR/RFA were comparable (94.4, 64.5, 51.3, and 51.3% vs. 87.5, 73.5, 45.7, and 40.0%, respectively, $P = 0.932$, Fig. 2b).

In addition, the corresponding 1-, 3-, 5-, 7-, and 10-year OS rates after initial resection between patients that received SLT and those that received RR/RFA were also similar (97.2, 83.3, 60.7, and 60.7%, vs. 98.8, 80.6, 68.9, 64.1, and 54.8%, respectively, $P = 0.614$, Fig. 2c).

DFS and OS by Recurrence Pattern

A significantly increased mean time to tumor recurrence and total number of relapse events were noted for the IM group compared to the MO group (1.65 ± 0.73 vs. 1.34 ± 0.67, $P = 0.026$; 39/75 vs. 12/47, $P = 0.004$) (Table 1).

The 1-, 3-, 5-, and 7-year DFS rates after retreatment were significantly lower in the IM group compared to the MO group, with rates of 66.9, 41.3, 31.8, and 31.8% and 81.8, 68.7, 68.7, and 68.7%, respectively, ($P = 0.008$, Fig. 3a).

Table 1 Baseline characteristics of patients who suffered IM and MO at recurrent stage

Variables	IM	MO	*P*
Number of patients (*n*)	75	47	
Age (years)	47.93 ± 11.10	49.96 ± 10.18	0.318
< 60 versus ≥ 60 years	64:11	38:9	0.515
Gender (male/female)	63:12	42:3	0.115
HBsAg (positive/negative)	67:8	44:3	0.528
HBV-DNA (positive/negative)[a]	37:38	24:23	0.852
AFP (≤ 400: > 400, ng/ml)	52:23	33:14	0.918
Child-Pugh class (*A*/*B*)	70:5	43:2	0.710
TBIL(umol/L)	15.23 ± 6.30	14.13 ± 6.05	0.349
ALT (IU/L)	42.36 ± 22.75	64.22 ± 67.05	0.015
ALB (g/L)	42.13 ± 4.57	42.17 ± 7.29	0.967
Crea (mmol/L)	76.77 ± 13.54	79.41 ± 27.71	0.488
PT (s)	12.05 ± 1.28	12.29 ± 2.77	0.522
INR	1.06 ± 0.11	1.05 ± 0.17	0.647
MELD score	8.60 ± 1.54	8.68 ± 1.94	0.800
WBC (10^9/L)	5.06 ± 1.78	4.94 ± 1.87	0.681
PLT (10^9/L)	116.11 ± 56.15	120.09 ± 47.95	0.535
Tumor characteristics at recurrent stage			
Number of tumors (single/multiple)	51:24	36:11	0.307
Diameter of tumor (cm)			
Mean	3.49 ± 2.30	3.96 ± 3.27	0.366
≤5 versus >5	63:12	37:10	0.461
Milan criteria (within/beyond)	52:23	46:11	0.384
MVI (presence/absence)	27:48	5:42	0.002
Differentiation, *n* (%)			< 0.001
High	–	22	Per design
Moderate	28	25	
Low	47	–	Per design
Cirrhosis[b] (yes vs. no)	68:7	44:3	0.739
Type of retreatment (SLT vs. RR/RFA)	17:58	19:28	0.036
Mean intraoperative bleeding (mL)	544.93 ± 537.18	668.51 ± 571.72	0.230
Transfusion (yes vs. no)	9:66	8:39	0.533
Hospital stays (days)	9.36 ± 8.20	10.28 ± 6.21	0.436
Mean time to recurrence from retreatment (months)	19.71 ± 16.11	25.96 ± 21.71	0.074
Total times of recurrence	1.65 ± 0.73	1.34 ± 0.67	0.026
Mean follow-up time from retreatment (months)	26.85 ± 18.27	33.26 ± 21.51	0.084
No. of recurrence after retreatment, *n*	39	12	0.004
No. of death, *n* (%)	34	3	< 0.001

HBsAg hepatitis b surface antigen, *HBV* hepatitis b virus, *AFP* alpha-fetoprotein, *TBIL* total bilirubin, *ALT* alanine aminotransferase, *ALB* serum albumin., *PT* prothrombin time, *INR* international normalized ratio, *MELD* model for end-stage liver disease, *PLT* platelet, *WBC* white blood cell, *BCLC* Barcelona Clinic Liver Cancer, *MVI* microvascular invasion, *SLT* salvage liver transplantation, *RR* repeat resection, *RFA* radiofrequency ablation

[a]Positive: HBV-DNA ≥ 10^3 copies/ml, negative: HBV-DNA < 10^3 copies/ml

[b]Cirrhosis, yes: Ishak: 5–6, no: Ishak < 5

During the median follow-up period of 22.3 months after retreatment, 34 patients in the IM group and 3 patients in the MO group died ($P < 0.001$, Table 1). The HCC patients in the MO group also exhibited significantly better OS rates compared to patients in the IM group (1-, 3-, 5-, and 7-year OS rates after retreatment: 83.3, 57.4, 22.9, and 22.9% vs. 100, 91.7, 91.7, and 73.4%, respectively, $P < 0.001$, Fig. 3b). The 1-, 3-, 5-, 7-, and 9-year OS rates after initial resection in the MO group were 100, 97.9, 95.1, 95.1, and 84.5%, which were significantly higher than those of patients in the

Table 2 Clinical data of primary treatment and tumor characteristics at initial stage

Variables	IM ($n = 75$)	MO ($n = 47$)	P
Mean time to recurrence from initial resection(months)	13.59 ± 14.74	32.26 ± 22.98	< 0.001
Mean follow-up time from initial resection(months)	41.41 ± 24.18	66.66 ± 25.79	< 0.001
Type of resection* (major/minor)	11:64	8:39	0.727
Mean intraoperative bleeding (mL)	346.89 ± 186.98	416.30 ± 238.29	0.078
Transfusion (yes vs. no)	3:72	4:43	0.427
Hospital stays (days)	7.43 ± 3.51	7.74 ± 2.89	0.620
Tumor characteristics at initial stage			
Number of tumors (single/multiple)	59:16	39:8	0.560
Diameter of tumor (cm)			
Mean	3.15 ± 1.27	3.21 ± 0.91	0.752
≤3	42	25	
3–5	33	22	0.762
MVI (presence/absence)	14:61	11:36	0.528
Differentiation, *n* (%)			
High	5	3	0.001
Moderate	47	14	Per design
Low	23	30	
Cirrhosis (yes vs. no)	68:7	41:6	0.550

* Major resection = resection of three or more segments

IM group (97.3, 69.3, 43.1, 37.0, and 31.7%, respectively, $P < 0.001$, Fig. 3c).

Subgroup Analysis by Retreatment for Patients with MO and IM Recurrence

To evaluate the effects of different retreatment strategies on patient survival, subgroup analysis was performed between MO and IM patients (Fig. 4).

For MO patients, DFS rates after retreatment in the SLT group were significantly better than those in the RR/RFA group (1-, 3-, and 5-year DFS rates: 94.4, 87.7, and 87.7% and 72.8, 52.4, and 52.4%, respectively, $P = 0.017$, Fig. 4a). However, the 1-, 3-, 5-, and 7-year OS rates after retreatment for SLT and RR/RFA were 100.0, 84.8, 84.8, and 84.8% and 100.0, 100.0, 100.0, and 75.0%, respectively, which were not significantly different ($P = 0.366$, Fig. 4b).The OS rates after initial resection were also comparable between SLT and RR/RFA (1-, 3-, 5-, and 7-year OS rates: 100.0, 100.0, 88.0, and 88.0% and 100.0, 100.0, 100.0, and 87.5%, respectively, $P = 0.154$, Fig. 4c).

For patients with IM, no significant difference in DFS after retreatment was found between SLT and RR/RFA treatments. The 1-, 3-, and 5-year DFS rates after retreatment for SLT and RR/RFA were 87.4, 50.3, and 50.3% and 64.6, 39.5, and 27.7%, respectively, ($P = 0.187$, Fig. 4d). Additionally, the 1-, 3-, and 5-year OS rates after retreatment with SLT and RR/RFA were 87.8, 41.5, and 0.0% and 81.9, 63.0, and 45.7%, respectively, which were not significantly different ($P = 0.111$, Fig. 4e).The OS rates after initial resection were also comparable between SLT and RR/RFA (1-, 3-, 5-, and 7-year OS rates: 94.1, 70.6, and 16.5% and 98.3, 69.3, 50.4, and 43.2%, respectively, $P = 0.077$, Fig. 4f).

Prognostic Factors for Patients with Recurrent HCC After Retreatment

OS Univariate analysis revealed that differentiation of the primary tumor ($P = 0.010$), HBsAg ($P = 0.038$), AFP level ($P = 0.002$), recurrence pattern ($P = 0.035$), recurrent tumor diameter ($P = 0.031$), within the Milan criteria ($P = 0.009$), and MVI ($P = 0.025$) were significant independent prognostic factors for OS. Further multivariate analysis confirmed that differentiation of the primary tumor [low hazard ratio (HR) = 2.010, 95% confidence interval (CI): 1.023–3.952, $P = 0.043$], AFP level (≥ 400 ng/ml, HR = 2.572, 95% CI: 1.240–5.334, $P = 0.011$), recurrence pattern (MO, HR = 0.093, 95% CI: 0.026–0.337, $P < 0.001$) and MVI (presence, HR = 5.425, 95% CI: 2.519–11.683, $P < 0.001$) at the recurrent stage were significant independent prognostic factors for OS (Table 3).

DFS Univariate analysis indicated that the following five variables were statistically significant prognostic factors associated with DFS in patients with recurrent HCC:

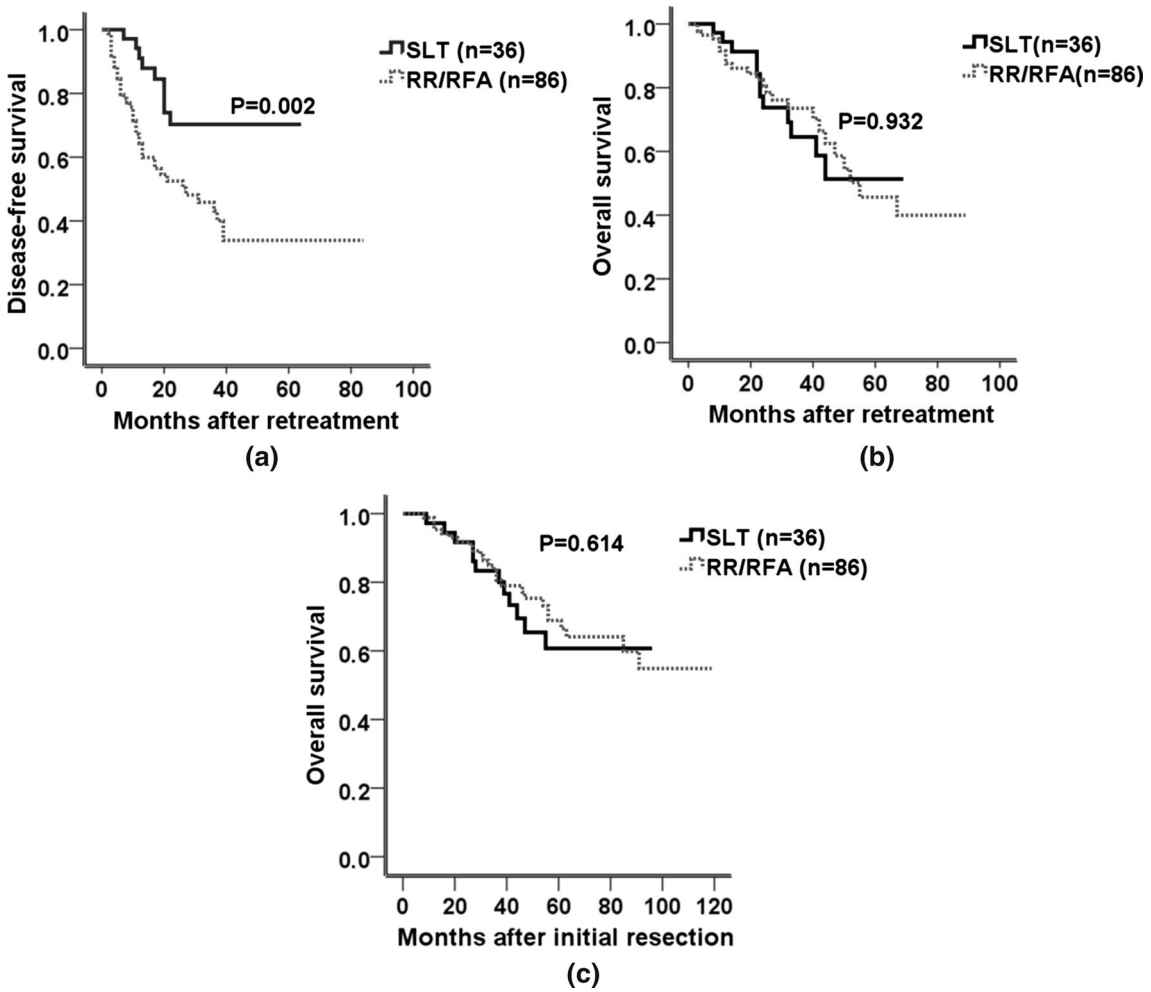

Fig. 2 Disease-free survival and overall survival by retreatment type. **a** Disease-free survival after retreatment between the SLT group and the RR/RFA group; **b** overall survival after retreatment between the SLT group and the RR/RFA group; **c** overall survival after initial resection between the SLT group and the RR/RFA group

type of resection at the initial stage ($P = 0.020$), recurrence pattern ($P = 0.001$), type of retreatment (SLT vs. RR/RFA, $P = 0.001$), differentiation of the recurrent tumor ($P = 0.009$), and cirrhosis ($P = 0.020$). Furthermore, according to the multivariate analysis, the type of initial resection (major, HR = 2.766; 95% CI: 1.312–5.829; $P = 0.007$), recurrence pattern (MO, HR = 0.318, 95% CI: 0.125–0.810, $P = 0.016$), the type of retreatment (RR/RFA, HR = 3.334; 95% CI: 1.546–7.188; $P = 0.002$), and cirrhosis (yes, HR = 7.688; 95% CI: 1.031–57.319; $P = 0.047$) remained independent prognostic factors of DFS (Table 4).

Discussion

In this study, we demonstrated that the long-term survival of patients with an MO recurrence pattern was significantly higher than that of patients with IM pattern, which is consistent with previous reports [11–13, 17, 19, 20, 24]. After classifying intrahepatic recurrent HCC patterns based on the histopathological standard, we recommend SLT as the preferred option for patients with intrahepatic recurrent HCC due to better DFS, especially for MO patients.

Unfortunately, no "gold standard" is available to distinguish IM and MO. Although DNA sequencing has been used previously, this procedure does not always differentiate the clone origin of various recurrent lesions, largely due to tumor heterogeneity among multiple lesions or even within the same lesion [25, 26]. As a standard and feasible method in clinical studies, the histopathological approach is frequently used to distinguish IM and MO [17, 20, 24, 27]. Therefore, the histopathological standard was applied to differentiate IM and MO in this study.

The two patterns of recurrence differ significantly in occurrence mechanism, time to relapse, and treatment response. Several studies have proposed that repeat hepatic

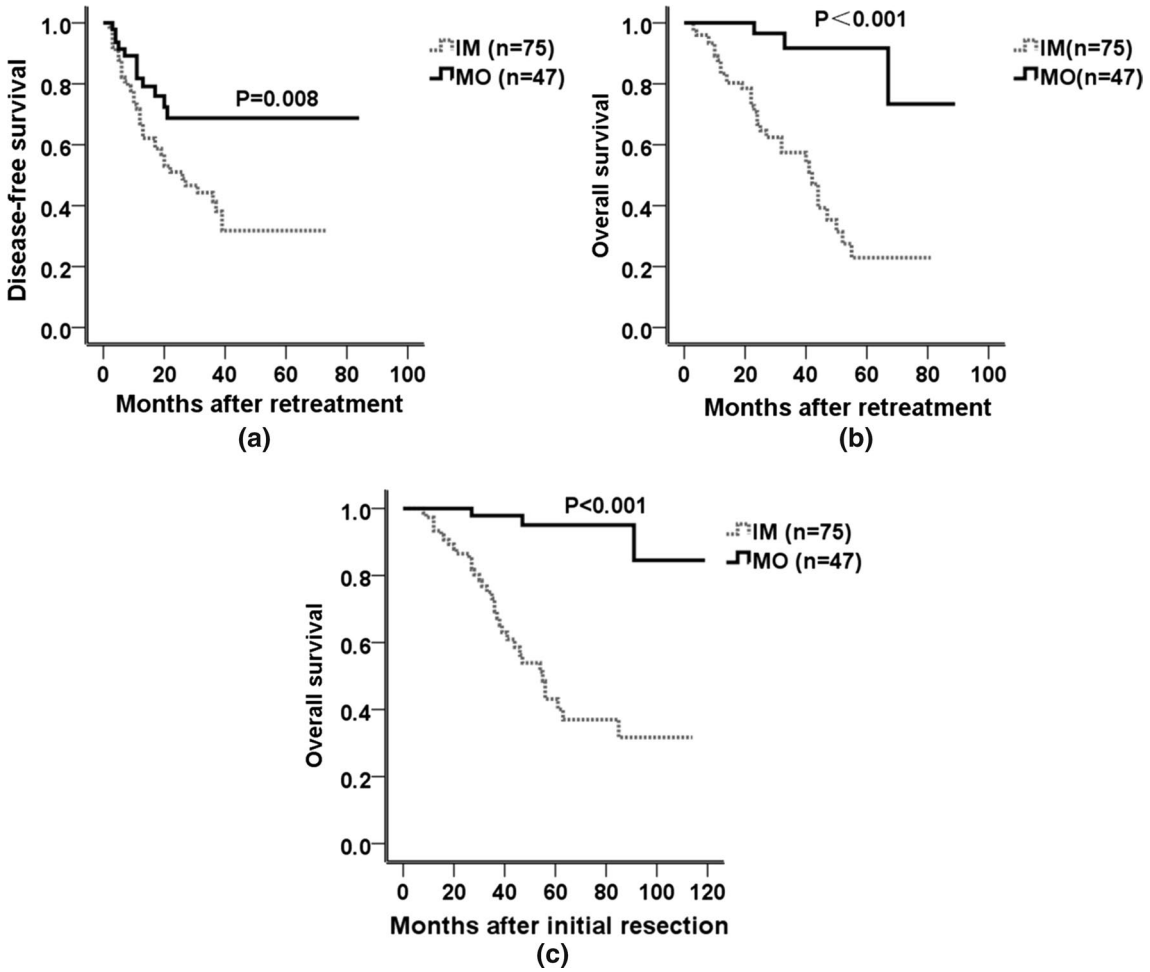

Fig. 3 Disease-free survival and overall survival by recurrent patterns. **a** Disease-free survival after retreatment between the IM recurrence and the MO recurrence; **b** overall survival after retreatment between the IM recurrence and the MO recurrence; **c** overall survival after initial resection between the IM recurrence and the MO recurrence

resection and ablation are good options for MO patients compared to IM patients. [11–13] Because the tumor behavior of early recurrent HCC is more biologically aggressive and a higher incidence of MVI was observed in the IM group than in the MO group in this study (Table 1), we and Jin et al. suggest that transarterial chemoembolization (TACE) might be as effective as RR or ablation for early recurrence [18, 28]. As de novo tumors, MO-recurrent tumors are similar to primary tumors in that DFS but not OS following primary liver transplantation was improved compared to treatment with primary liver resection or RFA (Fig. 4). However, there are no studies in the literature documenting the long-term outcomes of SLT and RR/RFA for patients with recurrent HCC according to recurrence pattern. Therefore, to our knowledge, this is the first study to compare the long-term outcomes of SLT and RR/RFA according to recurrence pattern.

In the past decade, a strategy of initial resection and SLT for intrahepatic recurrent HCC has been proposed as a suitable approach to treat early HCC with preserved liver function [29, 30]. The long-term survival outcomes of this strategy are comparable to those of primary liver transplantation [31]. However, the indications for SLT in patients with intrahepatic recurrent HCC have not been appropriately established. Based on the results of this study, we suggest the recommendation of SLT treatment for patients with the MO recurrence pattern. Considering the paucity of liver donors, this new surgical strategy optimizes the organ allocation policy and helps liver surgeon select potential recipients.

Only recurrence pattern was an independent prognostic factor for both OS and DFS in our study. Indeed, better DFS, less time to tumor recurrence, and a lower total number of relapse events were evident in MO patients compared to IM patients in this study. Due to the distinct prognosis

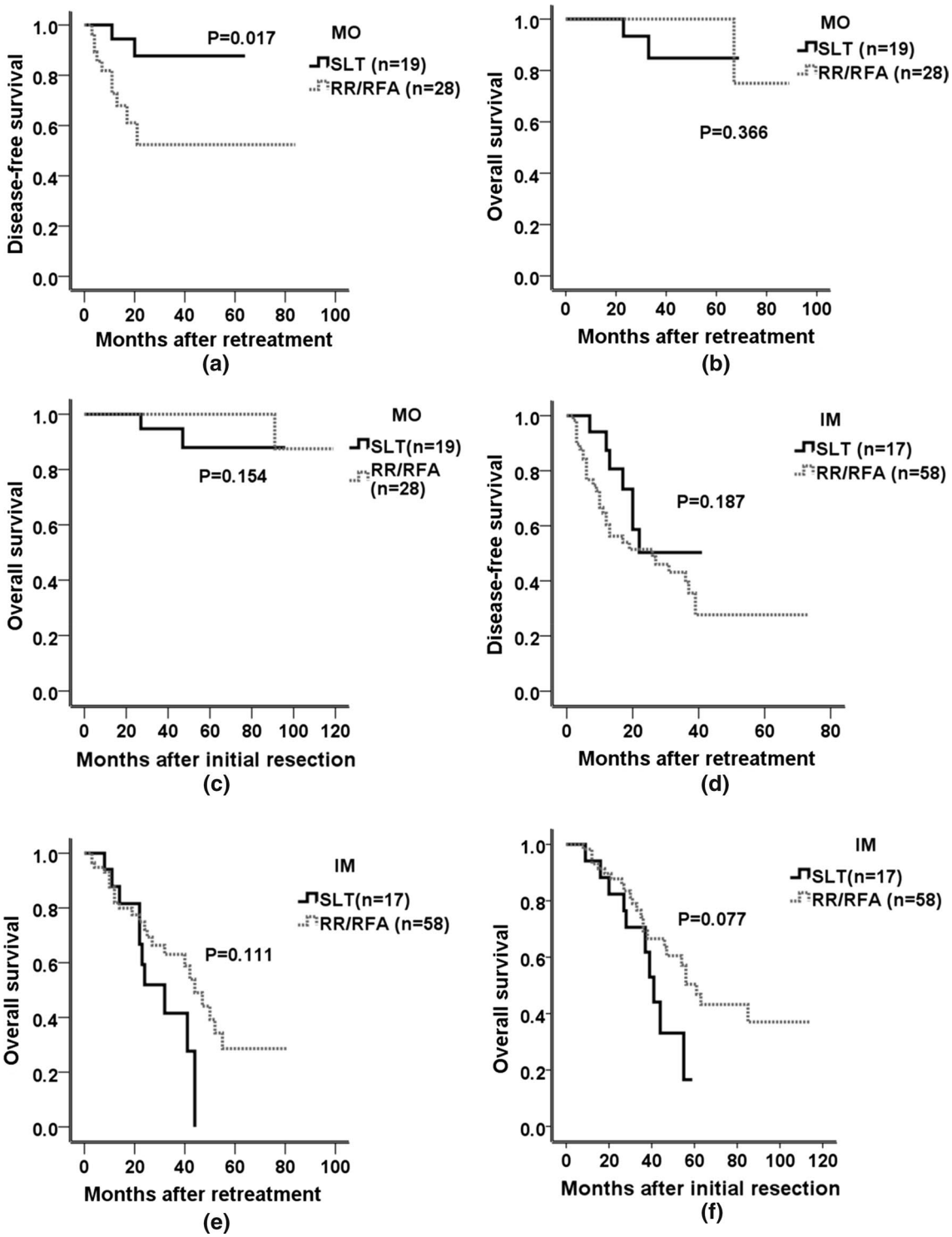

Fig. 4 Subgroup analysis by different retreatment for patients with IM and MO recurrence. **a** For MO recurrence, disease-free survival after retreatment between the SLT group and the RR/RFA group; **b** for MO recurrence, overall survival after retreatment between the SLT group and the RR/RFA group; **c** for MO recurrence, overall survival after initial resection between the SLT group and the RR/RFA group; **d** for IM recurrence, disease-free survival after retreatment between the SLT group and the RR/RFA group; **e** for IM recurrence, overall survival after retreatment between the SLT group and the RR/RFA group; **f** for IM recurrence, overall survival after initial resection between the SLT group and the RR/RFA group

Table 3 Univariate and multivariate analyses of prognostic factors for overall survival in patients with recurrent HCCs after retreatment

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Prognostic factor at initial stage				
Mean time to recurrence from initial resection	0.959 (0.903–1.018)	0.172		
Type of resection, major versus minor	1.547 (0.399–6.002)	0.528		
Differentiation, low versus moderate/high	6.510 (1.574–26.933)	0.010	2.010 (1.023–3.952)	0.043
Tumor number, multiple versus single	0.784 (0.300–2.051)	0.620		
Tumor size, 3–5 cm versus ≤ 3 cm	0.807 (0.277–2.351)	0.694		
Microvascular invasion, presence versus absence	0.975 (0.280–3.394)	0.968		
Prognostic factor at recurrent stage				
Gender (F vs. M)	0.633 (0.074–5.385)	0.675		
Age (≥ 60 vs. < 60 years)	1.200 (0.179–8.032)	0.851		
HBsAg (positive vs. negative)	18.296 (1.169–286.265)	0.038	3.086 (0.412–23.124)	0.273
HBV-DNA (Positive vs. Negative)	1.351 (0.403–4.534)	0.626		
AFP (≥ 400 vs. < 400 ng/mL)	3.017 (1.083–8.408)	0.035	2.572 (1.240–5.334)	0.011
TBIL	1.018 (0.717–1.445)	0.922		
ALT	0.999 (0.977–1.021)	0.914		
ALB	1.039 (0.958–1.126)	0.361		
Crea	0.999 (0.848–1.177)	0.988		
HGB	0.993 (0.956–1.032)	0.729		
PLT	1.007 (0.993–1.020)	0.331		
WBC	0.935 (0.597–1.465)	0.770		
PT	0.867 (0.591–1.272)	0.467		
MELD score	0.867 (0.694–1.085)	0.212		
Recurrent pattern, MO versus IM	0.002 (0.002–0.241)	0.002	0.093 (0.026–0.337)	< 0.001
Type of retreatment, RR/RFA versus SLT	0.853 (0.263–2.766)	0.791		
Transfusion, yes versus no	2.734 (0.653–11.446)	0.169		
Differentiation, high versus moderate/high	0.448 (0.092–2.177)	0.320		
Number of tumors, multiple versus single	1.124 (0.396–3.189)	0.826		
Diameter of tumor, >5 cm versus ≤ 5 cm	0.104 (0.013–0.813)	0.031	0.590 (0.182–1.912)	0.379
Milan criteria, beyond versus within	0.105 (0.019–0.576)	0.009	0.492 (0.186–1.912)	0.152
Microvascular invasion, presence versus absence	7.851 (2.617–23.548)	< 0.001	5.425 (2.519–11.683)	< 0.001
Cirrhosis, yes versus no	6.278 (0.376–104.903)	0.201		

and treatment effects between IM and MO, it is important to predict and distinguish IM and MO before surgery. As discussed above, this may improve surgical decision-making. Many clinical studies have investigated the distinct risk factors associated with IM and MO (summarized in Table 5) [17, 27, 32–34]. These risk factors can be divided into the following three categories: (1) host factors, such as HBV-DNA level and liver cirrhosis; (2) primary tumor factors, such as tumor size, number, and differentiation; and (3) surgery-related factors, such as perioperative blood transfusion and surgical technique/skills. According to previous studies, primary tumor factors are mainly associated with the IM recurrence pattern, whereas host factors are mainly associated with the MO recurrence pattern. However, a consensus has not been achieved. Further investigations are warranted to clarify this point.

This study has several limitations. First, given its retrospective design, a selection bias may be inherent. Second, the number of participants was relatively small, and the follow-up duration was short. In addition, in our study, most of the biopsies for intrahepatic recurrent HCC were surgical resection specimens, whereas others were percutaneous biopsies at the time of RFA. As different parts of a tumor can exhibit different characteristics, there may

Table 4 Univariate and multivariate analyses of prognostic factors for disease-free survival in patients with recurrent HCCs after retreatment

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Prognostic factor at initial stage				
Mean time to recurrence from initial resection	1.009 (0.985–1.034)	0.442		
Type of resection, minor versus major	2.718 (1.167–6.333)	0.020	2.766 (1.312–5.829)	0.007
Differentiation, low versus moderate/high	1.569 (0.748–3.291)	0.233		
Tumor number, multiple versus single	1.307 (0.568–3.010)	0.529		
Tumor size, 3–5 cm versus ≤ 3 cm	1.392 (0.661–2.934)	0.384		
Microvascular invasion, presence versus absence	1.308 (0.501–3.415)	0.583		
Prognostic factor at recurrent stage				
Gender (F vs. M)	1.309 (0.286–5.983)	0.728		
Age (≥ 60 vs. < 60 years)	1.506 (0.468–4.668)	0.478		
HBsAg (positive vs. negative)	1.683 (0.383–7.394)	0.490		
HBV-DNA (positive vs. negative)	1.026 (0.501–2.099)	0.944		
AFP (≥ 400 vs. < 400 ng/mL)	1.122 (0.557–2.257)	0.748		
TBIL	0.933 (0.728–1.196)	0.583		
ALT	0.996 (0.986–1.005)	0.348		
ALB	0.993 (0.932–1.058)	0.835		
Crea	0.982 (0.882–1.094)	0.740		
HGB	1.018 (0.994–1.042)	0.141		
PLT	1.000 (0.992–1.009)	0.939		
WBC	0.937 (0.705–1.245)	0.653		
PT	0.869 (0.665–1.135)	0.302		
MELD score	0.933 (0.789–1.104)	0.419		
Recurrent pattern, MO versus IM	0.097 (0.023–0.4050.)	0.001	0.318 (0.125–0.810)	0.016
Type of retreatment, RR/RFA versus SLT	4.941 (1.849–13.202)	0.001	3.334 (1.546–7.188)	0.002
Transfusion, yes versus no	1.014 (0.329–3.121)	0.981		
Differentiation, high versus moderate/high	0.287 (0.113–0.732)	0.009	0.644 (0.358–1.158)	0.142
Number of tumors, multiple versus single	1.049 (0.478–2.302)	0.904		
Diameter of tumor, >5 cm versus ≤ 5 cm	0.865 (0.188–3.968)	0.851		
Milan criteria, beyond versus within	1.410 (0.351–5.665)	0.628		
Microvascular invasion, presence versus absence	1.348 (0.582–3.124)	0.486		
Cirrhosis, yes versus no	14.527 (1.525–138.388)	0.020	7.688 (1.031–57.319)	0.047

be limitations in the interpretation of percutaneous biopsies to classify recurrence as MO versus IM. Furthermore, a randomized controlled study is needed to confirm the outcomes of SLT and RR/RFA according to recurrence pattern.

Conclusion

In conclusion, the MO pattern of intrahepatic recurrent HCC is associated with better long-term outcomes compared to the IM pattern. SLT is the preferred option for intrahepatic recurrent HCC, especially for MO cases.

Table 5 Risk factors related to intrahepatic metastasis (early recurrence) and multicentric occurrence (late recurrence)

Years	Authors	Type	Risk factors		
			Host factors	Primary tumor factors	Surgery-related factors
2000	Poon et al. [27]	Early		Preoperative tumor rupture, venous invasion	
		Late	Cirrhosis		
2003	Imamura et al. [32]	Early		MVI, AFP level	Non-anatomical resection
		Late	Higher grade of hepatitis activity	Multiple tumors, gross tumor classification	
2014	Du et al. [33]	Early		Multiple tumors venous infiltration	
		Late	ICG, serum albumin level HBeAg status		
2015	Cheng et al. [34]	Early		Tumor size absence of tumor capsule MVI	
		Late	Cirrhosis	AFP level	
2017	Hao et al. [15]	IM	High HBV-DNA load	Tumor size multiple tumors venous infiltration	Blood transfusion
		MO	High HBV-DNA load; cirrhosis; Ishak inflammatory activity		Blood transfusion

IM intrahepatic metastasis, *MO* multicentric occurrence, *MVI* microvascular invasion, *AFP* alpha-fetoprotein, *ICG* indocyanine green, *HBeAg* hepatitis b e antigen

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Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

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