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Early versus late recurrence of centrally located hepatocellular carcinoma after mesohepatectomy

A cohort study based on the STROBE guidelines

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Abstract

The aim of this study was to investigate the features, treatment, and prognosis of early versus late recurrence of centrally located hepatocellular carcinoma (CL-HCC) after mesohepatectomy (MH).

Three hundred forty eight patients with CL-HCC undergoing MH were included. Data on clinicopathological characteristics, initial surgical details, timing and sites of tumor recurrence, management after recurrence, and long-term outcomes were analyzed.

The optimal cutoff value to differentiate early (71 patients, 64.5%) versus late (39, 35.5%) recurrence was defined as 12 months. Patients with early recurrence (ER) had higher alpha fetoprotein (AFP) level ($P < .001$), more advanced tumor stage ($P = .024$), and higher incidence of microvascular invasion (MVI, $P = .001$). Patients with ER had higher incidence of local tumor recurrence ($P = .027$) and higher average number of recurrent nodules ($P = .016$) than patients with LR. Patients after ER showed a better overall survival (from date of diagnosis of recurrence) than after late recurrence (LR). Patients with ER had less chances of curative treatment (14.1% vs 41.0%, $P = .004$) after tumor recurrence than patients with LR. Multivariable analyses revealed that liver cirrhosis ($P < .001$) and tumor differentiation ($P < .001$) were associated with an increased likelihood of LR, while multiple tumor number ($P = .005$), type IV classification ($P = .012$), and MVI ($P < .001$) were independent risk factors related to ER.

ER and LR after MH for CL-HCC were associated with different risk predictors and prognosis. Data on the timing of recurrence may inform decisions about postoperative adjuvant treatment, as well as help to predict long-term survival for these patients.

Abbreviations: ALBI = albumin-bilirubin, CL-HCC = centrally located hepatocellular carcinoma, CT = computed tomography, DFS = disease-free survival, EH = extended hepatectomy, HCC = hepatocellular carcinoma, ICG-R15 = indocyanine green retention rate at 15 minutes, MH = mesohepatectomy, MRI = magnetic resonance imaging, MVI = microvascular invasion, OS = overall survival, RFA = radiofrequency ablation, TACE = transcatheter arterial chemoembolization.

Keywords: hepatocellular carcinoma, prognosis, recurrence

1. Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide.[1] Liver resection is considered the most potentially curative treatment modality for HCC patients when liver transplantation is unavailable.[2] For patients with centrally located hepatocellular carcinoma (CL-HCC), both extended hepatectomy (EH) and mesohepatectomy (resection of Couinaud segments IV, V, and VIII ± I) can be carried out.[3–5] However, mesohepatectomy (MH) should be a priority in patients with impaired liver function secondary to the underlying liver cirrhosis.[6–8] Though technically challenging, MH can preserve >35% functional liver volume compared with EH (e.g., hemihepatectomy and trisegmentectomy).[8] In addition, a previous study has shown a better long-term overall survival (OS) in CL-HCC patients after MH compared with patients after EH. In this study, the better OS in the MH group was due to the higher possibility to receive further curative treatment after tumor recurrence.[9] However, even after resection with curative intent, the long-term survival for patients with CL-HCC after MH still remained unsatisfactory.[9–11] The main reason for the poor long-term oncological outcomes was associated with the high incidence of tumor recurrence.

Centrally located liver tumors included a large series of patients with various tumor characteristics and treatment modalities. The risk of tumor recurrence after MH may be generally related to series of clinical and biological parameters (e.g., tumor location, number, size, resected volume, tumor differentiation, and microvascular invasion).[3,5,11–13] Additionally, the etiology of tumor recurrence was related to either intrahepatic metastasis from the initial tumor or a *de novo* tumor. In theory, recurrence by primary tumor metastasis took place in the early period after liver resection, while late recurrence tumors were more often multicentric or de novo lesions in the remnant liver.[14] In previous studies, early tumor recurrence after hepatectomy for

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HCC has been reported to be related to certain tumor pathological characteristics, whereas late recurrence was associated with underlying liver disease such as liver cirrhosis.[15–19]

To our knowledge, few reports have focused on the risk factors and managements associated with tumor recurrence in an exclusive cohort of patients with CL-HCC after MH. In the present study, we aimed to explore the risk factors, patterns of recurrence, and outcomes in these patients with early versus late recurrence (ER vs LR). Owing to the large heterogeneity of tumor types or management within the CL-HCC, we classified the included patients into 4 subgroups based on our previously established classifications for patients with CL-HCC.

2. Patients and methods

2.1. Study population

We retrospectively reviewed 880 consecutive patients who underwent liver resection for CL-HCC between January 2012 and October 2017 in West China Hospital, Sichuan University. Five hundred thirty two patients were excluded due to the following reasons: patients with recurrent tumors undergoing reoperation (n = 23); patients with concurrent peripherally located tumors (n = 83); patients undergoing extended hepatectomy (n = 92); patients without R0 resection (n = 6); tumors only requiring resection of one Couinaud segment (n = 145); history of preoperative treatment including transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA), or chemoradiotherapy (n = 88); history of other malignant tumors (n = 15); and incomplete clinicopathologic data (n = 80). Data of the remaining 348 patients were analyzed in detail. The HCC diagnosis was confirmed by histopathology. This study was approved by Ethical Committee of our hospital.

Liver function should meet the criterion for hepatectomy: indocyanine green retention rate at 15 minutes (ICG-R15) below 15%. In addition, according to the study of Johnson et al,[20] the Albumin-Bilirubin (ALBI) grade was utilized to evaluate liver function for patients with CL-HCC. As described before, patients with CL-HCC were divided into 4 groups based on the classification (Fig. 1).

2.2. Surgical procedures

The hepatic vascular ultrasonography, contrast-enhanced thoracic, abdominal and pelvic computed tomography (CT), and/or magnetic resonance imaging (MRI) were performed before surgery. The intraoperative ultrasound was routinely performed after liver mobilization. Surgical procedures related to MH were described before.[9,13] Before hepatectomy, portal pedicles of the resected side were dissected and ligated, and branches of the preserved side were encircled for latter exclusion. For MH, the left medial and right anterior portal pedicles were usually divided for selective hepatic inflow control. Liver parenchyma transection was carried out under the guidance of intraoperative ultrasonography. Harmonic scalpel (Ethicon Endo-Surgery, Minnesota), cavitron ultrasonic aspiration (CUSA, Valleylab, Inc., Minnesota), and or LigaSure (ValleyLab, Inc., Minnesota) were used for transection of hepatic parenchyma.

2.3. Definitions

In this study, MH procedures included standard MH (IV + V + VIII), irregular MH (V + IVb or VIII + IVa), minor MH (V + VIII or IVa + IVb), and extended MH (IV + V + VIII + I). Definition of anatomic resection was based on the study of Shindoh et al.[21] Microvascular invasion (MVI) was defined as vascular (vein or artery) or lymphatic invasion (identification of tumor cells within endothelial-lined spaces on standard hematoxylin and eosin stained slides).[22] Liver cirrhosis was diagnosed based on histopathologic examination of the specimens. The time of OS was calculated from the date of surgery to the last follow-up or until death. The time of disease-free survival (DFS) was calculated from the date of surgery to the date of tumor recurrence (confirmed by imaging findings or biopsies). According to Shindoh et al,[21] local recurrence was defined as any recurrence inside the treated segment (the residual part) or recurrence close to the cut surface of the liver at the time of the initial recurrence, irrespective of the presence of simultaneous recurrences in other parts of the liver.

The treatment strategy for tumor recurrence was evaluated based on liver function, patient's performance status and tumor burden including location, size, number, and residual liver volume. Treatment with curative intent, including rehepatectomy, ablation or both, was considered for some patients with intrahepatic recurrence. Other treatment modalities including TACE, RFA, and chemoradiotherapy were individualized for patients with advanced recurrent disease.

2.4. Statistical analysis

Continuous variables were presented as mean ± SD and tested by *t* test or Kruskal–Wallis H test when appropriate. Categorical variables were expressed as number (%) and tested by chi-square test or Fisher exact test. The OS and DFS curves were determined by the Kaplan–Meier method and compared by the Log-rank test. Multivariate Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for ER versus LR in patients with CL-HCC. Variables with P values $<.1$ in univariable analysis were entered into the multivariable model. P value $<.05$ was deemed statistically significant. All statistical analyses were performed by R (http://www.R-project.org) and EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc., Boston, MA).

3. Results

3.1. Optimal cutoff value for early and late recurrence

Patients were followed up at a 2-month interval in the first year after discharge from hospital and at a 3-month interval thereafter. Based on our results, tumor recurrence was confirmed by imaging examinations or biopsies. Twelve months was defied as the optimal cut-off value, as shown in Supplementary Fig. 1, http://links.lww.com/MD/D17.

3.2. Characteristics of patient with tumor recurrence

Basic characteristics of patients in 2 groups were shown in Table 1 in detail. With a median follow-up of 20 (range, 1–72) months, 110 of 348 patients (31.6%) experienced recurrences, including 71 within 12 months and 39 after 12 months. Patients in ER group had higher alpha fetoprotein (AFP) level ($P < .001$), more advanced tumor stage ($P = .024$), and higher incidence of microvascular invasion (MVI, $P = .001$). Other parameters related to preoperative liver function and tumor burden showed no significant differences (all P values $>.05$).

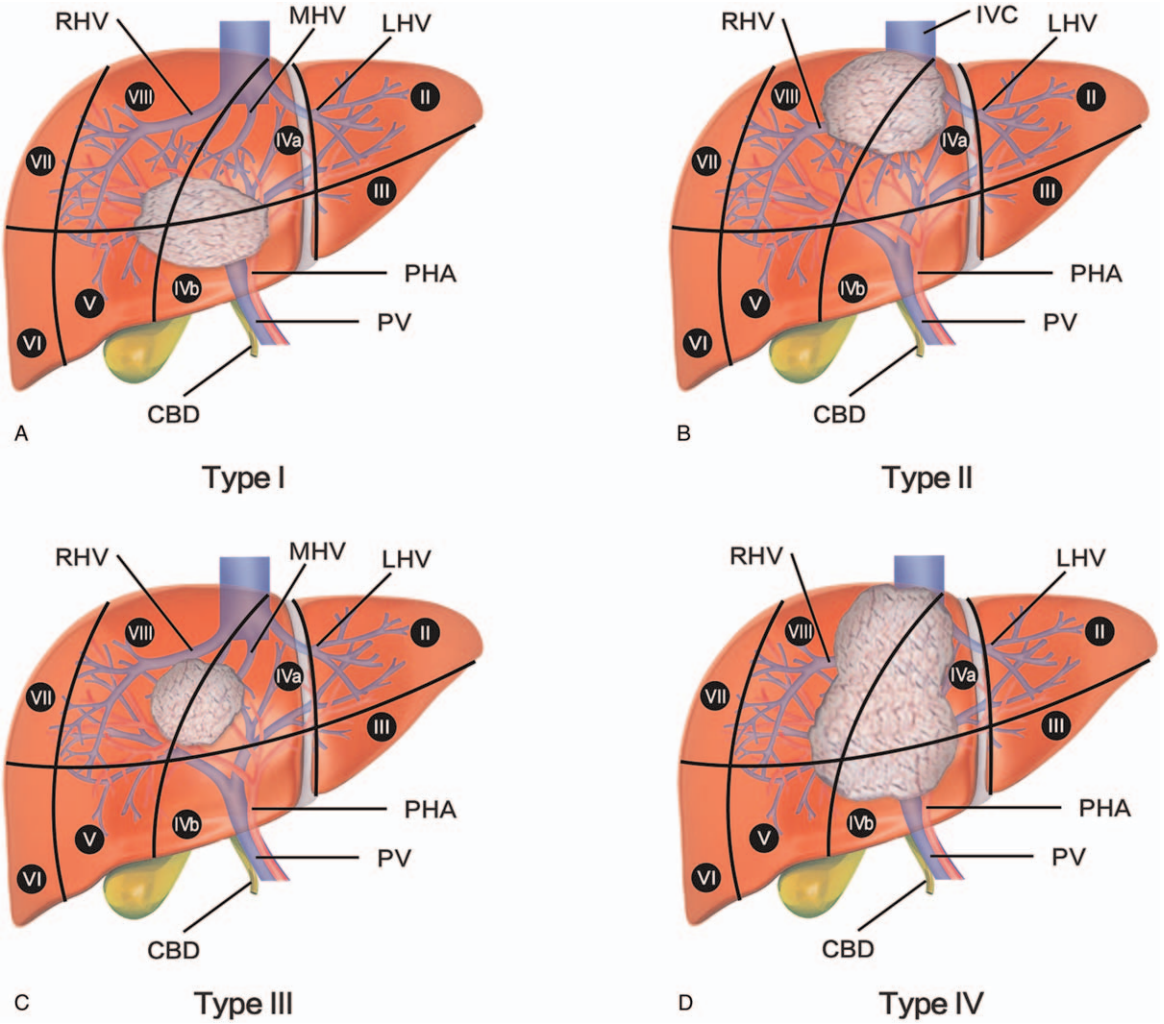

Figure 1. Classification of centrally located hepatocellular carcinoma: A type I, B type II, C type III, and D type IV. CBD = common bile duct, IVC = inferior vena cava, LHV = left hepatic vein, MHV = middle hepatic vein, PHA = proper hepatic artery, PV = portal vein, RHV = right hepatic vein.

Mean time to tumor recurrence in the original population was significantly shorter (5.0 ± 0.3 months vs 22.3 ± 1.1 months, $P < .001$) in ER group. The average number of recurrent nodules tended to be higher ($P = .016$) in ER group than in LR group. Patients with ER had higher incidence of local tumor recurrence ($P = .027$) than patients with LR. No significant differences were observed in recurrent tumor size ($P = .965$) and incidence of concurrent extra-hepatic recurrence ($P = .915$) (Table 1).

3.3. Treatment and outcomes of patients with tumor recurrence

In the original population, cumulative 1-, 3- and 5-year OS rates were 87.9%, 75.0%, and 64.8%, respectively. Patients after ER showed a better OS (from date of diagnosis of recurrence) than after LR (Fig. 2). The median survival time after recurrence were 12 months in ER group and 52 months in LR group, respectively ($P = .0028$). Patients with ER had less chances of curative treatment (14.1% vs 41.0%, $P = .004$) after tumor recurrence than patients with LR (Table 1). Ten patients in ER group underwent curative treatment (liver resection, 7; ablation, 2; liver transplantation, 1), while 16 patients in LR group were indicated for curative treatment (liver resection, 12; ablation, 3; liver transplantation, 1). Patients undergoing curative treatment (1-, 3-, and 5-year OS rates were 96.0%, 87·1%, and 58.0%, respectively) had a better OS compared with patients after non-curative treatment and no-treatment (1-, 3-, and 5-year OS rates were 69.1%, 41·0%, and 30.1%, respectively) (Supplementary Fig. 2, http://links.lww.com/MD/D17). In contrast, the 1-, 3-, and 5-year OS rates of patients treated with curative intent for their recurrence were not statistically different from that of 94.1%, 89.3%, and 89.3% among patients who never experienced a recurrence.

In addition, patients in ER group who underwent curative treatment had a similar OS (from time of recurrence) compared with patients in LR group after curative treatment (data not shown).

3.4. Risk factors related to ER and LR

As shown in Table 2, in univariable analyses, factors associated with ER after initial hepatectomy were investigated among 309 patients in the analyzed cohort. Factors related to LR were investigated among the 277 patients who were free of recurrence

Table 1

Clinical features of patients with tumor recurrence.

	ER (n = 71)	LR (n = 39)	*P*-value
Sex female/male	5/66	5/34	.322
Age, y	52.2 ± 10.8	54.1 ± 12.7	.432
ICG-R15%	6.9 ± 5.4	6.2 ± 4.0	.731
Preoperative ALT, IU/L	59.9 ± 61.7	54.1 ± 45.6	.609
Preoperative AST, IU/L	58.3 ± 54.9	51.7 ± 33.4	.496
Preoperative total bilirubin, μmol/L	20.6 ± 28.4	21.0 ± 30.6	.390
Preoperative albumin, g/L	40.3 ± 3.9	41.2 ± 3.7	.260
ALBI Grade 1/2/3	25/43/3	16/22/1	.876
Preoperative platelet 109/L	140.5 ± 59.1	120.6 ± 59.5	.093
Preoperative prothrombin time, s	12.4 ± 0.9	12.3 ± 1.1	.845
AFP, ng/mL	763.3 (1.3–15594.0)	126.9 (0.8–1210.0)	<.001
HBsAg P/N	66/5	34/5	.322
HBV-DNA copies/mL <1000/≥1000	24/40	21/18	.105
Tumor size, cm	6.6 ± 3.0	5.8 ± 2.8	.186
Tumor number single/multiple	45/26	29/10	.240
Classification I/II/III/IV	20/19/15/17	10/9/8/12	.887
T-stage T1/T2/T3	47/12/12	35/2/2	.024
Liver cirrhosis yes/no	53/18	33/6	.332
Duration of operation, min	173.1 ± 42.8	173.5 ± 36.8	.964
Intraoperative blood loss, mL	486.8 ± 355.4	424.2 ± 479.0	.476
Duration of vascular exclusion, min	34.0 ± 16.1	31.8 ± 21.8	.729
Intraoperative transfusion, mL no/yes	46/12	29/4	.396
Transfusion volume, mL	206.0 ± 499.0	137.9 ± 401.8	.504
Postoperative hospital stay, d	13.3 ± 4.1	12.6 ± 6.3	.523
Anatomic resection yes/no	59/12	33/6	1.000
MVI No/Yes	27/33	29/8	.001
Tumor encapsulation			.329
Encapsulated	45 (63.4%)	21 (53.8%)	
Nonencapsulated	26 (36.6%)	18 (46.2%)	
Differentiation high/moderate/low	11/36/24	8/24/7	.192
Tumor characteristics after recurrence			
Mean time to recurrence, mo	5.0 ± 0.3	22.3 ± 1.1	<.001
Local recurrence/non-local recurrence	33/38	9/30	.027
Recurrent tumor size, cm	2.5 ± 1.6	2.5 ± 1.1	.965
Recurrent tumor number multiple/single	46/17	17/18	.016
Coexisting extrahepatic metastasis	4 (5.6%)	2 (5.1%)	.915
Treatment after recurrence curative/non-curative/none	10/32/29	16/9/14	.004

Data are shown as mean ± SD or median (range) or n (%). AFP = alpha fetoprotein, ALBI = albumin-Bilirubin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ER = early recurrence, HBV = hepatitis B virus, ICG-R15 = indocyanine green retention rate at 15 min, LR = late recurrence, MVI = microvascular invasion, N = No, PV = portal vein, Y = Yes.

in the first 12 months after liver resection. Consequently, liver cirrhosis, type IV classification and tumor differentiation were risk factors related to late tumor recurrence (all *P* values <.05). ALBI grade 2 and grade 3, AFP level >400 ng/mL, positive HBsAg, tumor size ≥5 cm, multiple tumor number, type IV classification, later tumor stage, liver cirrhosis, intraoperative blood loss ≥800 mL, non-anatomic resection, and MVI were risk indicators for ER (all *P* values <.05).

Multivariable analyses revealed that liver cirrhosis ($P < .001$) and tumor differentiation ($P < .001$) were associated with an increased likelihood of late tumor recurrence, while multiple tumor number ($P = .005$), type IV classification ($P = .012$), and MVI ($P < .001$) were independent risk factors related to ER (Table 3).

4. Discussion

Both EH and MH can be performed in patients with CL-HCC, while parenchyma-sparing MH is sometimes considered the only feasible surgical option, due to the impaired liver function and limited volume of residual liver. Several previous reports have shown the long-term outcomes of patients with CL-HCC after MH.[9–11,23] Owing to a high incidence of tumor recurrence after MH, overall survival for patients with CL-HCC after MH is unsatisfactory. To our knowledge, few previous studies have reported risk factors related to tumor recurrence for patients with CL-HCC after MH. Owing to the heterogeneity of tumor parameters and related surgical procedures in CL-HCC after MH, the long-term prognosis for patients with CL-HCC after MH may be influenced by series of factors associated with tumor features (e.g., micro- or macro-vascular invasion), underlying liver function (e.g., cirrhosis), and surgical procedures (e.g., anatomic resection).

In this study, the classification system for CL-HCC was established according to the tumor position and the anatomical location of lesions relative to the intrahepatic vascular structures.[13,24] Based on this classification, CL-HCC can be grouped into 4 types, and each type was associated with a different surgical approach and outcomes.[24] In type I, segments V + IVb was usually be resected to achieve tumor clearance. In type II,

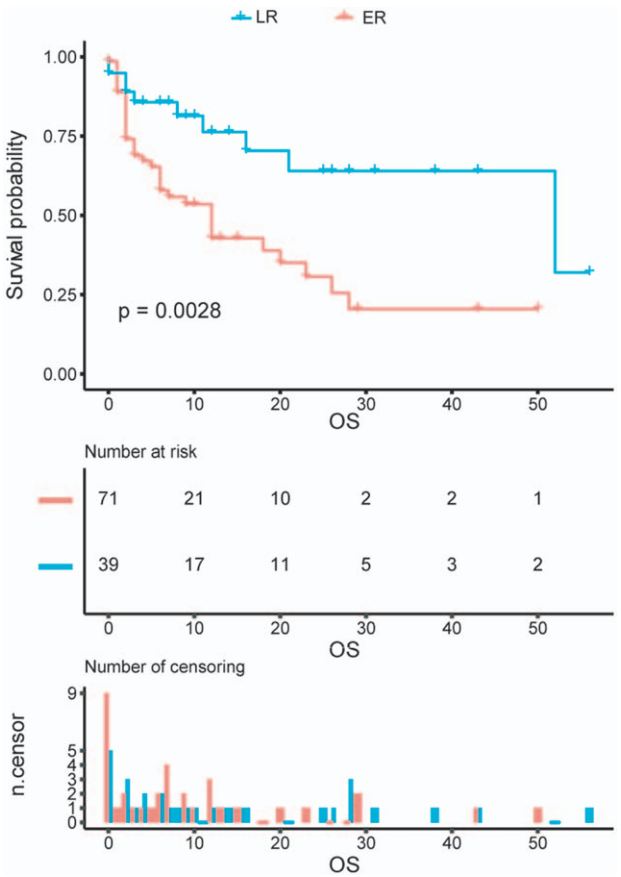

Figure 2. Survival outcomes (from recurrence date) for CL-HCC patients with early recurrence and late recurrence. CL-HCC = centrally located hepatocellular carcinoma.

Table 2

Univariable analysis of risk factors for early and late recurrence in patients with CL-HCC.

	ER (n = 71)		LR (n = 39)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex (male/female)	2.2 (0.9, 5.4)	.095	1.4 (0.5, 3.5)	.505
Age, y	1.0 (1.0, 1.0)	.101	1.0 (1.0, 1.0)	.692
ICG-R15 (≥10% vs <10%)	1.4 (0.4, 4.9)	.560	1.4 (0.7, 2.6)	.291
ALBI grade				
Grade 1	1	1	1	1
Grade 2	1.9 (1.1, 3.1)	.013	1.4 (0.7, 2.7)	.299
Grade 3	4.5 (1.4, 14.9)	.014	1.0 (0.1, 7.9)	.976
Preoperative platelet 109/L	1.0 (1.0, 1.0)	.304	1.0 (1.0, 1.0)	.183
AFP (≥400/<400 ng/mL)	2.4 (1.5, 3.8)	<.001	1.2 (0.4, 4.0)	.735
HBsAg (P/N)	2.8 (1.1, 6.9)	.028	1.7 (0.7, 4.4)	.260
HBV-DNA (≥1000/<1000 copies/mL)	1.6 (1.0, 2.7)	.054	1.0 (0.5, 1.8)	.902
Tumor size (≥5/<5 cm)	2.1 (1.3, 3.5)	.004	1.3 (0.6, 2.6)	.506
Tumor number multiple/single	2.1 (1.3, 3.4)	.003	0.2 (0.0, 1.8)	.156
Classification				
I	1	1		
II	2.1 (1.1, 3.9)	.025	2.0 (0.8, 5.0)	.131
III	0.9 (0.4, 1.7)	.663	1.0 (0.4, 2.5)	.962
IV	2.8 (1.5, 5.4)	.002	4.6 (1.9, 10.9)	.001
T-stage				
T1	1	1	1	1
T2	2.9 (1.6, 5.6)	.001	0.8 (0.2, 3.4)	.768
T3	5.2 (2.7, 9.8)	<.001	4.2 (1.0, 17.7)	.053
Liver cirrhosis yes/no	4.6 (2.4, 8.5)	<.001	2.8 (1.3, 6.2)	.010
Duration of operation, min	1.0 (1.0, 1.0)	.710	1.0 (1.0, 1.0)	.403
Intraoperative blood loss (≥800/<800 mL)	2.6 (1.4, 4.6)	.002	1.3 (0.4, 3.6)	.662
Duration of vascular exclusion, min	1.0 (1.0, 1.0)	.678	1.0 (1.0, 1.0)	.903
Anatomic resection (no/yes)	3.0 (1.6, 5.7)	.001	1.5 (0.5, 4.2)	.462
MVI (yes/no)	5.6 (3.3, 9.3)	<.001	1.1 (0.9, 1.3)	.549
Tumor encapsulation (nonencapsulated/encapsulated)	1.5 (0.8, 2.8)	.210	1.4 (0.6, 3.1)	.462
Differentiation (high/low)	0.4 (0.1, 2.6)	.318	2.1 (1.0, 4.2)	.043

Data was presented as HR (95% CI) *P*-value. AFP = alpha fetoprotein, ALBI = albumin-bilirubin, CL-HCC = centrally located hepatocellular carcinoma, ER = early recurrence, HBV = hepatitis B virus, ICG-R15 = indocyanine green retention rate at 15 min, LR = late recurrence, MVI = microvascular invasion, N = negative, P = positive.

segments V + IVb should be resected. For patients in type III, segments IVa + IVb, segments V + VIII, or segments IV + V + VIII could be resected depending on the relative positions of tumors. Segment IV + V + VIII ± I should be resected in Type IV to obtain tumor clearance.[13]

Our results showed that type IV classification was associated with early tumor recurrence. This can be explained as follows: tumors in type IV were often large enough or very close to the major central vascular and biliary structures, thus MH was difficult to carry out with adequate resection margins.[25] Many reports have shown that a resection margin smaller than 1 cm was a poor prognostic factor for long-term survival.[26–28] Tumors in type IV often had an advanced tumor burden and MH procedures in this type were also more challenging, which usually needed complicated vascular exclusion techniques such as infra-hepatic and supra-hepatic inferior vena cava exclusion.[24] As such, special attention should be paid to CL-HCC patients in type IV, especially in the first one year after MH. In addition to classification, risk factors including tumor size and MVI were associated with ER. Our results were in accordance with previous outcomes that ER was associated with adverse tumor factors.[14–16,18,19,29] As described before, early tumor recurrence may be the result of intrahepatic metastasis, microsatellite lesions or even residual disease that was present at the time of the first surgery. These results are extremely important for the potential use of some adjuvant treatments including postoperative TACE, and target therapy such as sorafenib in selected high-risk CL-HCC patients after MH.

Consistent with previous studies, in this study, liver cirrhosis was found to be a risk factor indicating late tumor recurrence.[15–18] Our result confirmed the conclusion that liver cirrhosis was related to multicentric carcinogenesis. HCC usually develops on a background of chronic liver inflammation and cirrhosis, particularly cirrhosis associated with hepatitis B virus and hepatitis C virus infections. An increased rate of random mutations in proliferative hepatocytes is one of the main mechanisms in HCC development from cirrhotic patients.[30] Mechanisms between ER and LR were different, while strictly distinguishing multicentric carcinogenesis and metastasis based on clinical observation is difficult and it should be explored in molecular level.

Similar to former reports,[14–16,18] our results showed that CL-HCC patients with ER had a worse OS (from the recurrent date) compared with those with LR. An explanation for the finding can

Table 3

Multivariable analysis of risk factors for early and late recurrence in patients with CL-HCC.

	ER (n = 71)		LR (n = 39)	
	Hazard ratio	*P*-value	Hazard ratio	*P*-value
Tumor size (≥5/<5 cm)				
Tumor number (multiple/single)	2.808 (1.373–5.743)	.005		
Classification				
I	1			
II	2.205 (0.821–5.927)	.117		
III	1.803 (0.699–4.653)	.223		
IV	3.204 (1.294–7.928)	.012		
Liver cirrhosis (yes/no)			6.738 (2.083–21.803)	<.001
Tumor differentiation (high/low)			4.907 (1.441–16.708)	<.001
MVI (yes/no)	8.870 (4.408–17.849)	<.001		

Data were presented as HR (95% CI) *P*-value. CL-HCC = centrally located hepatocellular carcinoma, ER = early recurrence, LR = late recurrence, MVI = microvascular invasion.

be that patients with ER had more advanced tumor burden, thus it had less possibility for further curative treatment. Our results showed that patients undergoing curative retreatment had a better OS compared with those without curative treatment. Interestingly, patients with ER after curative treatment had a similar OS in comparison with those with LR. Moreover, patients who experienced tumor recurrence after curative-intent retreatment achieved similar post-recurrence survival compared with those without tumor recurrence. Consequently, if feasible, curative retreatments should be considered for patients with both ER and LR.[14]

There are several limitations in this study. First, it is a retrospective study with inherent selection bias. In addition, as a single-center study, this conclusion should be validated in other liver surgery centers. Finally, the effect of the classification in the present study is established mainly based on our experience and surgical outcomes. Though we have validated its prognostic significance in previous study, potential feasibility of this classification in CL-HCC still needs to be explored.

In conclusion, ER and LR after MH for CL-HCC were associated with different risk predictors and prognosis. The identification of risk factors for ER and LR after MH may provide some insights into the origins of recurrence and is important in determining strategies to prevent recurrence after surgery. The pattern of recurrence (ER or LR) and the probability of curative treatments after recurrence were related to the long-term prognosis. Data on the timing of recurrence may inform decisions about postoperative adjuvant treatment, as well as help to predict long-term survival for these patients.

Author contributions

Jie Mao proposed the study; Wei Li, Jun Zhao, and Jie Mao performed the research and wrote the first draft; Wei Li and Jun Zhao collected and analyzed the data; Jie Mao is the guarantor; all authors contributed to the design and interpretation of the study and to further drafts, and have read and approved the final version to be published.

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Validation: Wei Li, Jie Mao.
Visualization: Wei Li.
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Writing – review & editing: Wei Li.

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