Early versus late recurrence of centrally located hepatocellular carcinoma after mesohepatectomy: A cohort study based on the STROBE guidelines

Jun Zhao, MD, Wei Li, MD, Jie Mao, MD,∗

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 = .011). 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.[] Liver resection is considered the most potentially curative treatment modality for HCC patients when liver transplantation is unavailable.[] For patients with centrally located hepatocellular carcinoma (CL-HCC), both extended hepatectomy (EH) and mesohepatectomy (resection of Couinaud segments IV, V, and VIII[5]) 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.[10–11] 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).[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
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 management 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 chemotherapy (n = 88); history of other malignant tumors (n = 15); and incomplete clinicopathologic data (n = 80). 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 ultrasonography 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 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 rehapatectomy, 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 defined 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).
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.
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 $\geq 5$ cm, multiple tumor number, type IV classification, later tumor stage, liver cirrhosis, intraoperative blood loss $\geq 800$ 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).

**Table 1**

| Clinical features of patients with tumor recurrence. | ER (n=71) | LR (n=39) | P-value |
|------------------------------------------------------|-----------|-----------|---------|
| Sex female/male                                      | 56/6      | 5/34      | .322    |
| Age, y                                               | 52.2±10.8 | 54.1±12.7 | .432    |
| HBsAg P/N                                            | 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, $\mu$mol/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±69.1| 120.6±58.5| .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 $<1000/\geq1000$                   | 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/V/N                                 | 20/15/17  | 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±6.1  | 12.6±6.3  | .523    |
| Anatomic resection yes/no                            | 59/12     | 33/9      | 1.000   |
| MVI No/Yes                                           | 27/33     | 20/8      | .001    |
| Tumor encapsulation                                  | 45 (63.4%)| 21 (53.8%)| .192    |
| Encapsulated                                         | 26 (36.6%)| 18 (46.2%)|         |
| Differentiation high/moderate/low                    | 11/36/24  | 8/24/7    | .192    |
| Postoperative hospital stay, d                       | 13.3±6.1  | 12.6±6.3  | .523    |
| Anatomic resection yes/no                            | 59/12     | 33/9      | 1.000   |
| MVI No/Yes                                           | 27/33     | 20/8      | .001    |

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.

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.\cite{19,11,23} 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.\cite{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.\cite{24} In type I, segments V+IVb was usually resected to achieve tumor clearance. In type II,
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.\textsuperscript{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.\textsuperscript{13,25} Many reports have shown that a resection margin smaller than 1 cm was a poor prognostic factor for long-term survival.\textsuperscript{26–29} Tumors in type IV often had an advanced tumor burden and MH procedures in this type were also more challenging, which type IV often had an advanced tumor burden and MH was usually needed complicated vascular exclusion techniques such as infra-hepatic and supra-hepatic inferior vena cava exclusion.\textsuperscript{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 reports: \textsuperscript{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.\textsuperscript{13,16} 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.\textsuperscript{10} 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,\textsuperscript{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 2

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

|                | ER (n=71) | P value | LR (n=39) | P value |
|----------------|-----------|---------|-----------|---------|
| HR (95% CI)    |           |         |           |         |
| Sex (male/female) | 2.2 (0.9, 5.4) | .095 | 1.4 (0.5, 3.9) | .505 |
| Age, yr        | 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) | .364 | 1.0 (1.0, 1.0) | .163 |
| AFP (≥400/<400 ng/mL) | 2.35 (1.5, 3.8) | < .001 | 1.2 (0.4, 4.0) | .735 |
| HBsAg (u/mL)   | 2.5 (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) | .103 | 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 |           |         |           |         |
| I1             | 1         | 1       | 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             | 2.9 (1.6, 5.6) | .001 | 0.8 (0.2, 3.4) | .768 |
| T2             | 5.2 (2.7, 9.8) | < .001 | 4.2 (1.0, 17.7) | .053 |
| T3             | 4.6 (2.4, 8.5) | < .001 | 2.8 (1.3, 6.2) | .010 |
| Liver cirrhosis yes/no | 1.0 (1.0, 1.0) | .710 | 1.0 (1.0, 1.0) | .403 |
| Duration of operation, min | 1.0 (1.0, 1.0) | .002 | 1.3 (0.4, 3.6) | .662 |
| Intraoperative blood loss (≥800/<800 mL) | 2.6 (1.4, 4.6) | < .001 | 1.3 (0.4, 3.6) | .043 |
| 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 | 1.5 (0.8, 2.8) | .210 | 1.4 (0.6, 3.6) | .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. HR = 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.
Table 3
Multivariable analysis of risk factors for early and late recurrence in patients with CL-HCC.

|                      | ER (n=71) | P-value | LR (n=39) | P-value |
|----------------------|-----------|---------|-----------|---------|
| Tumor size (≥5/<5 cm) | 2.808 (1.373–5.743) | .005 | 6.738 (2.083–21.803) | <.001 |
| Tumor number (multiple/single) | I | 1 | 2.205 (0.821–5.927) | .117 |
| | II | 1.803 (0.609–4.653) | .223 |
| | III | 3.204 (1.294–7.926) | .012 |
| Liver cirrhosis (yes/no) | 8.870 (4.408–17.849) | <.001 |
| Tumor differentiation (high/low) |  |  | 4.907 (1.441–16.708) | <.001 |
| MH (yes/no) |  |  |  |  |

Data were presented as HR (95% CI). CL-HCC = centrally located hepatocellular carcinoma, ER = early recurrence, LR = late recurrence, MH = 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.

Conceptualization: Jun Zhao, Wei Li, Jie Mao.
Data curation: Jun Zhao, Wei Li, Jie Mao.
Formal analysis: Jun Zhao, Wei Li, Jie Mao.
Funding acquisition: Jun Zhao, Wei Li.
Investigation: Wei Li.
Methodology: Wei Li.
Project administration: Wei Li.

Resources: Wei Li.
Software: Wei Li.
Supervision: Wei Li, Jie Mao.
Validation: Wei Li, Jie Mao.
Visualization: Wei Li.
Writing – original draft: Wei Li.
Writing – review & editing: Wei Li.

References
[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[2] Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–2.
[3] Scudamore CH, Buczkowski AK, Shayan H, et al. Mesohepatectomy. Am J Surg 2000;179:356–60.
[4] Poon RT, Fan ST, Lo CM, et al. Extended hepatic resection for hepatocellular carcinoma in patients with cirrhosis: is it justified? Ann Surg 2002;236:602–11.
[5] Hu RH, Lee PH, Chang YC, et al. Treatment of centrally located hepatocellular carcinoma with central heptectomy. Surgery 2003;133:251—6.
[6] Gumbs AA, Gayet B. Totally laparoscopic central heptectomy. J Gastrointest Surg 2008;12:1153.
[7] Lee JG, Choi SB, Kim KS, et al. Central bisectionectomy for centrally located hepatocellular carcinoma. Br J Surg 2008;95:990–5.
[8] Mehrabi A, Mood ZA, Rashbazi N, et al. Mesohepatectomy as an option for the treatment of central liver tumours. J Am Coll Surg 2008;207:499–509.
[9] Li W, Li L, Minigalin D, et al. Anatomic mesohepatectomy versus extended heptectomy for patients with centrally located hepatocellular carcinoma. HPB (Oxford) 2018;20:530–7.
[10] Chen X, Li B, He W, et al. Mesohepatectomy versus extended heptectomy for centrally located hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2014;13:264–70.
[11] Yang LY, Chang RM, Lau WY, et al. Mesohepatectomy for centrally located large hepatocellular carcinoma: indications, techniques, and outcomes. Surgery 2014;156:1177–87.
[12] Wu CC, Ho WL, Chen JT, et al. Mesohepatectomy for centrally located hepatocellular carcinoma: an appraisal of a rare procedure. J Am Coll Surg 1999;188:509–15.
[13] Qin J, Wu H, Bai Y, et al. Mesohepatectomy for centrally located liver tumours. Br J Surg 2013;100:1620–6.
[14] Zhang XF, Beal EW, Bagante F, et al. Early versus late recurrence of intrahepatic cholangiocarcinoma after resection with curative intent. Br J Surg 2017;104:549–56.
[15] Li SH, Guo ZX, Xiao CZ, et al. Risk factors for early and late intrahepatic recurrence in patients with single hepatocellular carcinoma without macrovascular invasion after curative resection. Asian Pac J Cancer Prev 2013;14:4739–43.
[16] Cheng Z, Yang P, Qu S, et al. Risk factors and management for early and late intrahepatic recurrence of solitary hepatocellular carcinoma after curative resection. HPB (Oxford) 2015;17:422–7.
[17] Sasaki K, Shindoh J, Margonis GA, et al. Effect of background liver cirrhosis on outcomes of hepatectomy for hepatocellular carcinoma. JAMA Surg 2017;152:e165059.

[18] Imamura H, Matsuyma Y, Tanaka E, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 2003;38:200–7.

[19] Wu JC, Huang YH, Chau GY, et al. Risk factors for early and late recurrence in hepatitis B-related hepatocellular carcinoma. J Hepatol 2009;51:890–7.

[20] Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015;33:530–9.

[21] Shindoh J, Makusuchi M, Matsuyma Y, et al. Complete removal of the tumor-bearing portal territory decreases local tumor recurrence and improves disease-specific survival of patients with hepatocellular carcinoma. J Hepatol 2016;64:594–600.

[22] Parfitt JR, Marotta P, Alghamdi M, et al. Recurrent hepatocellular carcinoma after transplantation: use of a pathological score on explanted livers to predict recurrence. Liver Transpl 2007;13:543–51.

[23] Chen CH, Huang TH, Chang CC, et al. Central hepatectomy still plays an important role in treatment of early-stage centrally located hepatocellular carcinoma. World J Surg 2017;41:2830–7.

[24] Qiu J, Chen S, Wu H, et al. The prognostic value of a classification system for centrally located liver tumors in the setting of hepatocellular carcinoma after mesohepatectomy. Surg Oncol 2016;25:441–7.

[25] Miao XY, Hu JX, Dai WD, et al. Null-margin mesohepatectomy for centrally located hepatocellular carcinoma in cirrhotic patients. Hepatogastroenterology 2011;58:375–82.

[26] Shi M, Gao RP, Lin XJ, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg 2007;245:36–43.

[27] Regimbeau JM, Kianmanesh R, Farges O, et al. Extent of liver resection influences the outcome in patients with cirrhosis and small hepatocellular carcinoma. Surgery 2002;131:311–7.

[28] Lau H, Fan ST, Ng IO, et al. Long term prognosis after hepatectomy for hepatocellular carcinoma: a survival analysis of 204 consecutive patients. Cancer 1998;83:2302–11.

[29] Feng J, Wu J, Zhu R, et al. Simple risk score for prediction of early recurrence of hepatocellular carcinoma within the Milan criteria after orthotopic liver transplantation. Sci Rep 2017;7:44036.

[30] Tarao K, Hoshino H, Shimizu A, et al. Role of increased DNA synthesis activity of hepatocytes in multicentric hepatocarcinogenesis in residual liver of hepatectomized cirrhotic patients with hepatocellular carcinoma. Jpn J Cancer Res 1994;85:1040–4.