ORIGINAL ARTICLE

# Anatomic mesohepatectomy versus extended hepatectomy for patients with centrally located hepatocellular carcinoma

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## Abstract

**Background:** Both mesohepatectomy (MH) and extended hepatectomy (EH) can be performed for centrally located hepatocellular carcinoma (HCC). In this study, the long-term prognosis of these surgical approaches was assessed in patients with HCC.

**Methods:** A retrospective review was undertaken of 171 HCC patients who underwent anatomic hepatectomy for centrally located HCC between January 2005 and January 2016 in West China Hospital, Sichuan University. The impact of the surgical methods on prognosis was assessed for these patients by multivariable regression analysis. In addition, the patients in the MH group were matched in a 1:2 ratio with EH controls.

**Results:** In non-adjusted models, patients in the MH group had similar overall survival (OS, p = 0.066) and disease free survival (DFS, p = 0.654) compared to EH patients. After adjusting for all identified confounders, MH patients showed better OS in comparison with patients in the EH group (p = 0.001), while the DFS was similar. In the propensity score-matched (PSM) subset, patients in MH group had better OS (p = 0.033) but similar DFS (p = 0.328) compared to patients in the EH group.

**Conclusion:** Anatomic MH can be recommended as a reasonable surgical option in selected patients with centrally located HCC.

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## Introduction

For centrally located HCC (Couinaud's segments IV, V and VIII ± I), both extended hepatectomy (EH) and meso-hepatectomy (MH) can be performed.[1–3] EH, as a curative option for treatment of centrally located liver tumors, will theoretically increase the risk of post-operative morbidities such as liver failure owing to the extensive liver resection, especially for patients with cirrhotic livers or impaired liver function.[2,4] MH, a segment-oriented procedure, was first described by McBride and Wallace more than 40 years ago.[5] In this technique, the right anterior portal pedicle and the middle hepatic vein were usually removed with the liver parenchyma.[6] Compared to EH, more functional liver tissue can be retained by MH thereby decreasing the risk of post-operative liver failure.[7] MH may also allows the opportunity for a future repeat resection after tumor recurrence.[8,9] However, MH is technically challenging and often has a longer operative time, greater intra-operative blood loss and a higher risk of vascular and biliary complications.[9–14] In addition, another potential disadvantage of MH is compromise of surgical margins.[10,15]

Previous studies have assessed both short- and long-term prognosis of patients undergoing such surgery for centrally located HCC.[1–4,6,8–10,12–14,16–22] Past reports are inconsistent in their findings. Few studies have studied the independent role of the surgical methods (EH vs. MH) on the prognosis. Most of these studies enrolled patients with different clinicopathological features and MH and EH groups were often not comparable. Therefore, a simple prognostic comparison between

patients undergoing MH and EH would unavoidably introduce selection bias. To make patients in these two groups comparable, some studies have tried to adjust potential confounding factors by statistical methods such as multivariable regression analysis and propensity score matching.[9,13] However, some factors, which significantly influencing the prognosis of HCC patients, have not been adjusted in the models. For example, many studies have included patients with both anatomic and non-anatomic resections.[12,13,23] However, the oncologic advantage of anatomic resection (completely remove tumor-bearing portal territory) has been clarified in previous studies.[24–27] The present study, aimed to determine the prognostic difference of anatomic MH and EH for centrally located HCC, using more rigorous inclusion and exclusion criteria, and more efficient statistical methods.

## Patients and methods

A retrospective review was undertaken of 171 patients who underwent anatomic MH or EH for centrally located HCC between January 2005 and January 2016 in West China Hospital, Sichuan University. The HCC diagnosis was confirmed by histopathology. Patients were excluded from the initial cohort (604 patients with centrally located HCC) when meeting the following criterion: i) recurrent tumor and multiple tumors; ii) tumor greater than 5 cm; iii) tumor close proximity to, or direct invasion of, the first portal branch, the hepatocaval confluence (the second porta hepatis), or the inferior vena cava (IVC) and caudate lobe; iv) indocyanine green retention rate at 15 min $\geq$ 15% or Child-Pugh class B; v) anticipated liver remnant after liver resection more than 50% of functional liver volume; vi) patients who had gone other treatments (such as radiofrequency ablation and transarterial chemoembolization) before surgery; vii) patients undergoing R1 resection; viii) patients undergoing liver resection and intraoperative ablation (RFA); ix) patients undergoing non-anatomic surgery; x) history of other malignancy; xi) patients with extrahepatic diseases or other hepatic diseases unsuitable for surgery; xii) incomplete clinicopathologic data.

The remaining 171 patients in the cohort were classified into two subtypes: lesions arising from the junction between segments IVa and IVb, or between segments VIII and V were classified as type I, whereas lesions arising from the junction between segments IVa and IVb and segments VIII and V were classified as type II. For patients in type I, MH included anatomic resection of segments V + VIII or IVa + IVb, while EH included anatomic left or right hemi-hepatectomy. For patients in type II, MH included anatomic resection of segments V + VIII + IVa + IVb, while EH included anatomic left or right trisegmentectomy (Fig. 1). This study was approved by Ethical Committee of our hospital.

### Surgical procedures

Hepatic vascular ultrasonography, contrast-enhanced abdominal computed tomography (CT) and/or magnetic resonance imaging (MRI) were performed to evaluate tumor's relationship to vascular structures and to exclude intrahepatic or extrahepatic disseminated diseases. Intraoperative ultrasound was also routinely performed after liver mobilization. The choice of surgical methods (MH or EH) depended on a comprehensive evaluation of such tumor characteristics as size, location, underlying liver function and residual liver volume.

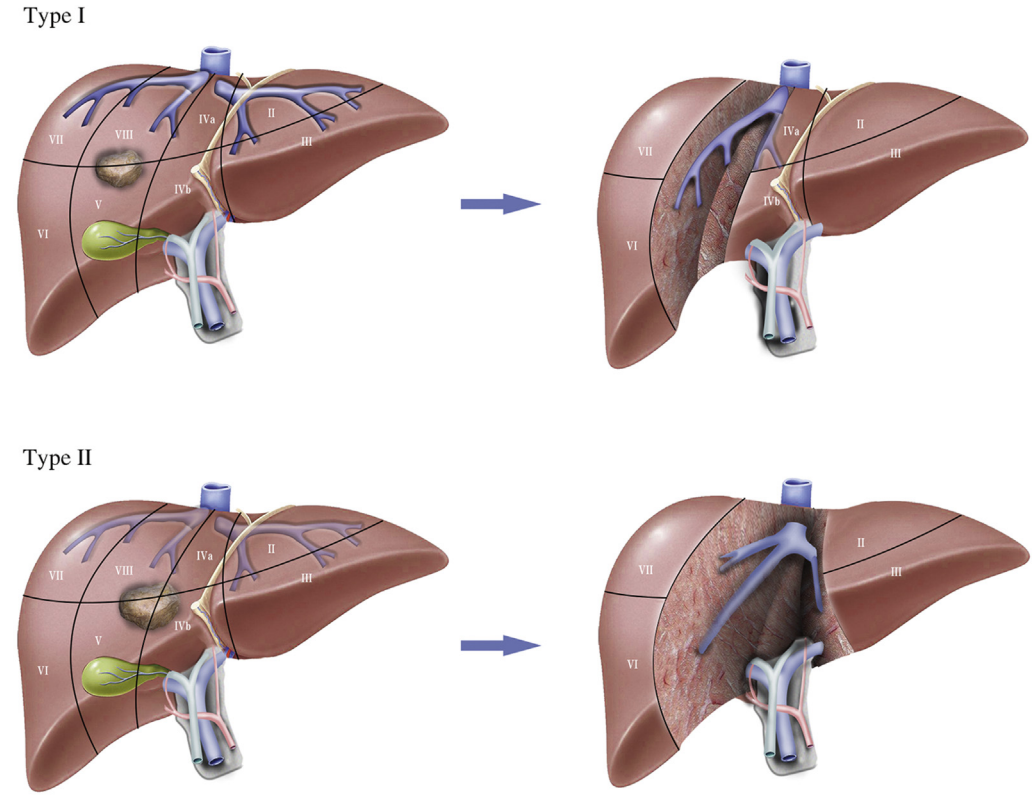
The surgical procedures have been previously described.[12,23,28] To ensure complete removal of the target part of the liver (anatomic resection), parenchymal transection is done from the segmental border to the landmark veins. Liver resection (both MH and EH) was undertaken by using the fissure for ligamentum teres hepatic (LTH) approach. In this approach, the round ligament is used as the symbol for isolating and dividing the Glisson's pedicles of the removed side. The anatomic landmarks for control of the inflow of the corresponding hepatic lobes or segments are shown in Supplementary Fig. 1.

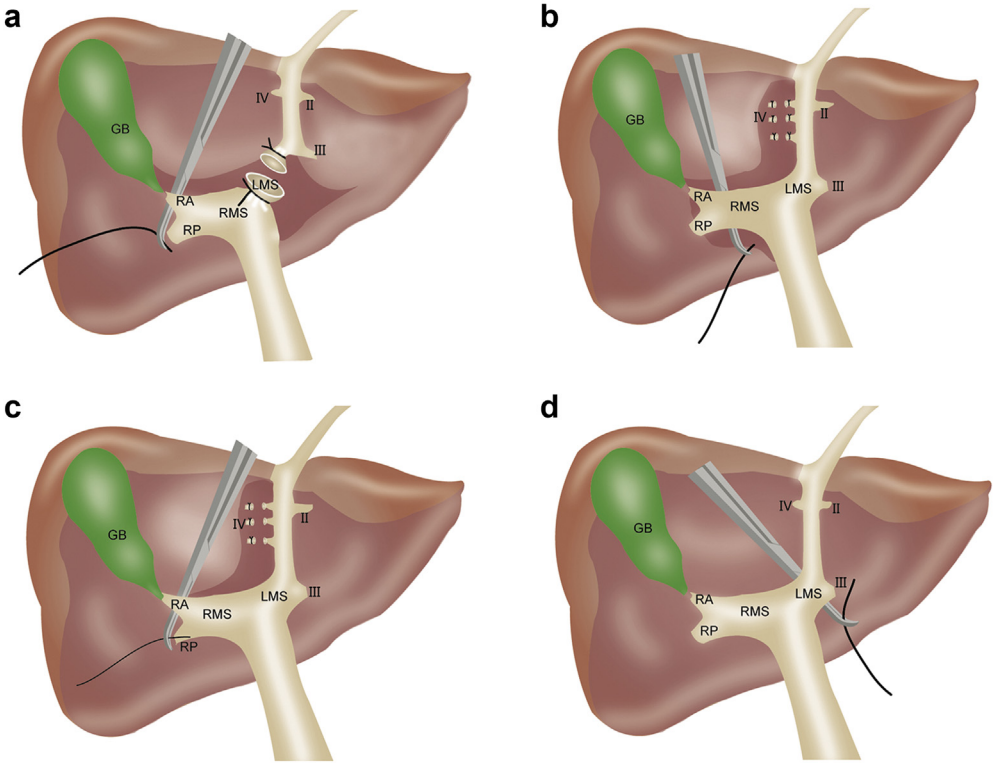
The LTH approach for hepatic trisegmentectomy has bee previously described (Fig. 1a,b).[28] For MH (IVa + IVb + V + VIII), the Glisson's pedicles to segment IV are cut along the right edge of the fissure for the round ligament firstly. The right anterior pedicle is isolated, encircled and clamped. Finally, the left resection line runs along the falciform ligament, and the right resection line along the demarcation line between the right anterior and the right posterior sectors (Fig. 1c).

For left hemihepatectomy, the inflow of the left lobe is blocked by dividing the left branch of the Glisson's pedicle. Firstly, an incision is made along the inferior margin of the quadrate lobe, above the transverse part of the fissure for the round ligament. A further incision is made in the confluence area of fissure for ligamentum teres and the left branch of the Glisson's pedicle. After these procedures, a long curved clamp is introduced from the incision left to the angular part of the fissure for the round ligament toward the right edge of the angular part of the fissure (a–d, Supplementary Fig. 1). Finally, the left branch of the Glisson's pedicle is divided and the hepatic parenchyma is transected (Fig. 1d). For right hemihepatectomy, the right Glisson's pedicle is also exposed at the hepatic hilum prior to resection without individually exposing the vessels in the hepatoduodenal ligament. To achieve anatomic resection, the middle hepatic vein on the cut surface of the liver should be fully exposed with the guidance of intraoperative ultrasound. Harmonic scalpel (Johnson & Johnson Corp. Princeton, NJ, USA) or cavitron ultrasonic aspiration (CUSA, Valleylab Corp. Somerville, NJ, USA) were used for transection of hepatic parenchyma.

### Definitions

Post-operative mortality was defined as death within 90 days after surgery. All complications were classified according to the Clavien-Dindo classification.[29] MVI was defined as invasion of either vascular (vein or artery) or lymphatic spaces, as evidenced by identification of tumor cells within endothelial-lined spaces on standard hematoxylin and eosin stained slides.[30] Ascites was



defined as abdominal drainage that was more than 500 ml/day and lasting longer than 3 days. Liver failure was defined as peak bilirubin concentration >7 mg/dL, peak international normalized ratio >2.0, encephalopathy or refractory ascites.[31] Bile leakage was defined as a drain fluid-to-serum total bilirubin concentration ratio ≥3.0.[32] Incisional and space/organ infection were defined according to Centers for Disease Control and Prevention (CDC)'s National Nosocomial Infection Surveillance (NNIS) system.[33] Recurrence was diagnosed by CT, MRI and/or ultrasonography during follow-up examination. The time of overall survival (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, when recurrence was confirmed by such imaging examinations as CT and MRI.

## Statistical analysis

Categorical variables are expressed as number (in %) and tested by Chi-square test or Fisher's exact test. Continuous variables are presented as mean ± SD and tested by T-test or Kruskal–Wallis H test when appropriate (Tables 1,2). The OS and DFS curves are determined, using the Kaplan–Meier method and compared, using the Log-rank test. By multivariate Cox proportional hazards regression models, Hazard ratios (HRs) and 95% confidence intervals (CI) are calculated for MH vs. EH in patients with centrally located HCC. The model I is adjusted for age, sex, ICG-R15, liver cirrhosis, tumor size, encapsulation, differentiation, MVI, HBsAg, AFP, blood loss, duration of operation and duration of vascular exclusion. The model II is adjusted for tumor size, encapsulation, differentiation and MVI (Tables 3,4). We adjusted for features that changed HR or β by at least 10%, when they were added to or removed from the model.[34] The interaction trend test was carried out by likelihood ratio test or Wald test for regression coefficients. Subgroup analysis was performed based on tumor types. Twelve patients comprised the patients in the MH group and are matched in a 1:2 ratio with EH controls. Matching is performed with the following variables: patient demographics (age, sex), tumor characteristics (tumor size, tumor encapsulation, tumor differentiation and MVI), and liver function (ICG-R15, liver cirrhosis). P value less than 0.05 was deemed statistically significant. Statistical analyses was performed by R (http://www.R-project.org) and EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc. Boston MA).

## Results

### Baseline characteristics

Demographic, clinical and surgical characteristics of 171 patients who underwent MH or EH for HCC, are summarized in Tables 1 and 2. More patients in the MH group had liver cirrhosis. Patients in MH group had longer operative time, vascular exclusion time and higher postoperative peak total bilirubin level.

**Table 1** Clinical features of the 171 patients with centrally located hepatocellular carcinoma

| | EH (n = 84) | MH (n = 87) | P-value |
|---|---|---|---|
| Sex female/male | 18/66 | 24/63 | 0.350 |
| Age (years) | 54.4 ± 9.2 | 53.0 ± 7.8 | 0.280 |
| ICG-R15 | 7.3 ± 2.3 | 7.3 ± 1.9 | 0.865 |
| Cirrhosis Y/N | 67/17 | 80/7 | 0.022 |
| Preoperative ALT (IU/L) | 56.4 ± 15.1 | 55.8 ± 16.5 | 0.797 |
| AFP (ng/ml) | 680 (8–1210) | 722 (8–1210) | 0.658 |
| HBsAg P/N | 70/14 | 74/13 | 0.757 |
| HBV-DNA Copies/mL | | | 0.991 |
| <1000 | 54 (64.3%) | 56 (64.4%) | |
| ≥1000 | 30 (35.7%) | 31 (35.6%) | |
| Tumor size (cm) | 4.1 ± 1.0 | 4.2 ± 0.9 | 0.759 |
| Tumor encapsulation | | | 0.458 |
| Encapsulated | 52 (61.9%) | 49 (56.3%) | |
| Nonencapsulated | 32 (38.1%) | 38 (43.7%) | |
| MVI | | | 0.933 |
| No | 74 (88.1%) | 77 (88.5%) | |
| Yes | 10 (11.9%) | 10 (11.5%) | |
| Differentiation high/moderate/low | 40/15/29 | 35/24/28 | 0.305 |

Data are shown as mean ± SD or median (range) or n (%). MH, mesohepatectomy; EH, extended hepatectomy; ICG-R15, indocyanine green retention rate at 15 min; ALT, alanine aminotransferase; AFP, alpha fetoprotein; HBV, hepatitis B virus; MVI, microvascular invasion. Y, Yes; N, No.

### Post-operative mortality and morbidity

In the MH group, post-operative complications included ascites in five patients, bile leakage in three patients, wound infection in four patients, organ/space infection in one patient and pulmonary infection in three patients, giving a post-operative morbidity rate of 18.4%. All complications settled on conservative management except in one patient who died from septic shock. In the EH group, post-operative complications included wound infection in three patients, pulmonary infection in two patients, bile leakage in two patients, liver failure in one patient and ascites in seven patients, for a post-operative morbidity rate of 17.9%. All these patients settled with conservative treatment and there were no deaths. There were no significant differences in morbidity and mortality rates between the two groups (both P > 0.05).

**Figure 1** Patients were classified into two subgroups (Type I and II) according to tumor locations and related procedures. a: Left trisegmentectomy using the LTH approach; b: Right trisegmentectomy using the LTH approach; c: Mesohepatectomy with the LTH approach d: Left hemihepatectomy with the LTH approach. LMS, left branch of Glisson's pedicle; RMS, right branch of Glisson's pedicle; GB, gallbladder; RA, right anterior branch of Glisson's pedicle; RP, right posterior branch of Glisson's pedicle

**Table 2** Surgical procedures and operation related parameters

| | EH (n = 84) | MH (n = 87) | P-value |
|---|---|---|---|
| Hepatectomy methods | | | |
| EH (REH/LEH) | 50/34 | / | |
| MH (IV + V + VIII/ V + VIII) | / | 51/36 | |
| Duration of operation (min) | 276 ± 53 | 311 ± 47 | <0.001 |
| Duration of vascular exclusion (min) | 32.4 ± 12.4 | 38.2 ± 15.9 | 0.009 |
| Intraoperative blood loss (ml) | 514.5 ± 169.8 | 558.9 ± 169.5 | 0.089 |
| Intraoperative transfusion (ml) | | | 0.385 |
| No | 76 (90.5%) | 75 (86.2%) | |
| Yes | 8 (9.5%) | 12 (13.8%) | |
| Postoperative peak ALT (IU/L) | 539.3 ± 202.4 | 567.0 ± 233.1 | 0.408 |
| Postoperative peak AST (IU/L) | 403.5 ± 177.7 | 390.9 ± 201.8 | 0.667 |
| Postoperative peak PT (s) | 15.5 ± 1.8 | 15.9 ± 1.9 | 0.194 |
| Postoperative peak TB (μmol/L) | 46.6 ± 18.5 | 53.8 ± 22.3 | 0.023 |
| Postoperative hospital stay (day) | 9.5 ± 3.1 | 9.8 ± 2.7 | 0.386 |
| 90-day mortality No/yes | 84/0 | 86/1 | 1 |

Data are shown as mean ± SD or n (%). MH, mesohepatectomy; EH, extended hepatectomy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; TB, Total bilirubin.

**Table 3** Associations of surgical approach with long-term survival

| | Non-adjusted | Model I | Model II |
|---|---|---|---|
| Overall survival | | | |
| Hepatectomy methods | | | |
| EH | 1 | 1 | 1 |
| MH | 0.7 (0.5, 1.0) 0.066 | 0.6 (0.4, 0.8) 0.001 | 0.5 (0.4, 0.8) 0.001 |
| Disease-free survival | | | |
| Hepatectomy methods | | | |
| EH | 1 | 1 | 1 |
| MH | 0.9 (0.7, 1.3) 0.654 | 0.9 (0.6, 1.2) 0.395 | 0.9 (0.6, 1.2) 0.354 |

Data was presented as HR (95%CI) P-value. Model I was adjusted for: Age, Sex, ICG-R15, Liver cirrhosis, Tumor size, Encapsulation, Differentiation, MVI, HBsAg, AFP, Blood loss, Duration of operation and Duration of vascular exclusion. Model II was adjusted for: Tumor size, Encapsulation, Differentiation and MVI. MH, mesohepatectomy; EH, extended hepatectomy.

**Table 4** Associations of surgical methods with overall survival and disease-free survival by subgroup analyses based on tumor locations

| | | Type I | Type II |
|---|---|---|---|
| Overall survival | Non-adjusted | | |
| | Hepatectomy methods | | |
| | EH | 1 | 1 |
| | MH | 0.7 (0.5, 1.2) 0.182 | 0.7 (0.4, 1.1) 0.166 |
| | Model I | | |
| | Hepatectomy methods | | |
| | EH | 1 | 1 |
| | MH | 0.4 (0.2, 0.8) 0.012 | 0.5 (0.3, 0.9) 0.018 |
| | Model II | | |
| | Hepatectomy methods | | |
| | EH | 1 | 1 |
| | MH | 0.5 (0.3, 0.8) 0.004 | 0.6 (0.4, 1.0) 0.055 |
| Disease-free survival | Non-adjusted | | |
| | Hepatectomy methods | | |
| | EH | 1 | 1 |
| | MH | 0.9 (0.6, 1.4) 0.642 | 1.0 (0.6, 1.5) 0.830 |
| | Model I | | |
| | Hepatectomy methods | | |
| | EH | 1 | 1 |
| | MH | 0.8 (0.5, 1.4) 0.406 | 0.7 (0.4, 1.2) 0.164 |
| | Model II | | |
| | Hepatectomy methods | | |
| | EH | 1 | 1 |
| | MH | 0.9 (0.5, 1.4) 0.530 | 0.9 (0.5, 1.5) 0.602 |

Data was presented as HR (95%CI) P-value. Model I was adjusted for: Age, Sex, ICG-R15, Liver cirrhosis, Tumor size, Encapsulation, Differentiation, MVI, HBsAg, AFP, Blood loss, Duration of operation and Duration of vascular exclusion. Model II was adjusted for: Tumor size, Encapsulation, Differentiation and MVI. MH, mesohepatectomy; EH, extended hepatectomy.

## Long-term outcomes of MH vs. EH in included patients

The median follow-up was 44 months (range 1–85). There was no significant difference in OS (Fig. 2a) between two groups (P = 0.057). The median OS in MH and EH groups was 48 and 37 months respectively. 1-, 3- and 5-years OS rates were 91.9%, 77.7% and 40.0% for the MH group and 89.3%, 51.4% and 29.3% for the EH group respectively Fig. 2b shows the DFS of patients in the two groups (P = 0.641). The median DFS in MH and EH groups was 33 and 29 months respectively. The 1-, 3- and 5-years DFS rates were 81.5%, 31.8% and 16.5% for MH group and 79.7%, 39.5% and 20.1% for EH group respectively.

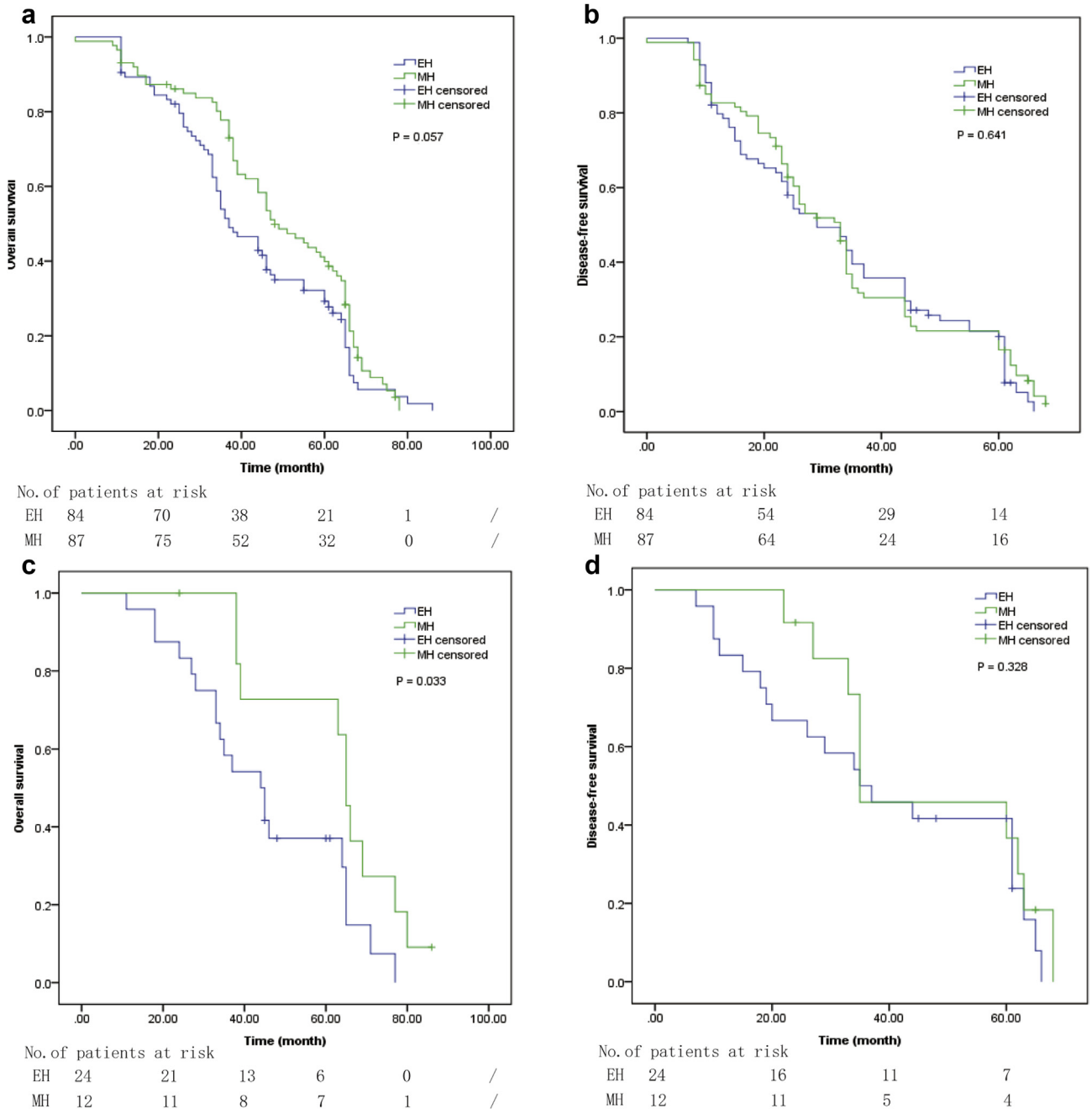



**Figure 2** a: Overall survival of MH vs. EH. b: Disease-free survival of MH vs. EH. c: Overall survival of MH vs. EH in the matched cohort. d: Disease-free survival of MH vs. EH in the matched cohort

### Independent role of MH vs. EH in OS and DFS for included patients

As is shown in Table 3, in a non-adjusted model, patients in the MH group had similar OS (HR: 0.7, 95%CI: 0.5–1.0, p = 0.066) and DFS (HR: 0.9, 95%CI: 0.7–1.3, p = 0.654) as patients in the EH group. After adjusting for all identified confounders in Model I, MH patients showed better OS compared to EH patients (HR: 0.6, 95%CI: 0.4–0.8, P = 0.001), while the DFS of the two groups was similar (HR: 0.9, 95%CI: 0.6–1.2, p = 0.395). Model II was adjusted only for tumor-related parameters, including tumor size, encapsulation, differentiation and MVI. Patients in the MH group had better OS (HR: 0.5, 95%CI: 0.4–0.8, P = 0.001) and similar DFS (HR: 0.9, 95%CI: 0.6–1.2, p = 0.354) compared with EH patients.

Table 4 shows the subgroup analysis, based on tumor types.

### Independent role of MH vs. EH in OS and DFS for patients in the matched cohort

Supplementary Tables 1 and 2 details perioperative parameters for the matched cohort. In the matched cohort, all covariates were similar, with p values >0.05. The distributions of propensity scores in the two matched groups were almost the same (data not shown). In the PSM cohort, patients in MH group showed better OS (P = 0.033) and similar DFS (P = 0.328) compared to patients in EH group (Fig. 2c,d).

## Discussion

In patients with centrally located HCC, the choice of surgical methods was predominately based on tumor characteristics such as size, location, underlying liver function and residual liver volume.[6,12–14] In the present study, to explore the independent role of surgical methods (anatomic MH vs. anatomic EH), we developed a strict inclusion criterion and adjusted several significant confounders (such as liver cirrhosis and liver function) using multivariable regression. Patients with major vascular invasion, non-anatomic resection, diameter more than 5 cm, and multiple lesions were excluded from the study.

In the present study, results showed that the blood loss and intraoperative transfusion were comparable between two groups. In our study, the mean operative time of 310.9 min for MH is comparable with other published studies.[6,12–14,20,21,35] Patients undergoing MH had significantly longer operative time owing to the complexity of this procedure. There are two hepatic resection planes and the operation fields are bordered by major structures, such as the bile duct and hepatic veins. It is well accepted that EH can cause serious complications, and liver failure is a major concern in major hepatectomy. However, no difference was found in morbidity and mortality rates between the two groups with no difference in bile leakage and liver failure rates. This may result from the limited patient numbers in this study. A high-quality randomized clinical trial, comparing the advantages and disadvantages of two surgical methods, is required, but it is difficult to perform.

According to tumor location, patients were divided into two subtypes in this study. Patients undergoing MH showed similar DFS but better OS in both subtypes. Because of the heterogeneity of the indications and follow-up periods, it is inappropriate to compare the long-term oncological outcomes in this study to previous reports. For patients in type I and II, both MH and EH can achieve anatomic resection. Though more liver parenchyma (the lateral sectors) was removed by EH, no significant differences were found in DFS. For patients undergoing MH, the chance for future treatment such as repeat resection, RFA and TACE increased and it may be the reason for a better OS in the MH group.[8,9] Miao *et al.* showed that recurrence after MH was mainly intrahepatic distant recurrence rather than transection edge recurrence.[15] As a result, we imagined that anatomic MH can achieve similar oncological outcomes compared to expanded hepatectomy in selected patients. Preserving non-tumorous liver parenchyma by MH may be a better choice for centrally located HCC with severe cirrhosis. Wide resection should be avoided, if possible, in treatment of small centrally located HCC. The strength of the current results lies in that the outcomes of MH and EH were confirmed by an adequate statistical method in a homogeneous, highly-selected population treated under the same surgical guideline with strict quality control of surgery. Besides, in the cohort with relatively small sample sizes, propensity score matching analysis allows balancing of a large number of covariates without the common statistical concerns.[36]

Anatomic MH was performed in the present study and achieved better OS compared to EH. For centrally located HCC, MH can secure a clean resection margin by exposure of the landmark veins at the cut surface when compared to EH. As an anatomic, oncologically radical but parenchyma-sparing hepatic resection, MH, can be recommended as a reasonable surgical option in selected patients with centrally located HCC. Admittedly, this study had several limitations, being retrospective and based in a single center. It may not be appropriate to generalize these results beyond specialized high-volume centers. There may also be other confounders and potential mediators that were not adjusted in our study models. Treatment after recurrence may have significantly influenced OS in both groups and we were unable to acquire these data. However, patients undergoing MH tended to have more opportunity for treatments such as reoperations, ablation and embolization. Finally, the inclusion of centrally located HCC patients with a strict criteria, may limit the applicability of our conclusions.

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#### Conflicts of interest

None to declare.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.hpb.2017.11.012.