Original Article

# One- versus two-stage partial hepatectomy for large resectable solitary hepatocellular carcinomas determined preoperatively to have a narrow resection margin: a propensity score matching analysis

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**Background:** For patients with a large but resectable solitary hepatocellular carcinoma (HCC) of >5 cm in diameter, it is often difficult to achieve a sufficient resection margin. There is still no study on whether a two-stage hepatectomy to increase a narrow resection margin would be beneficial.

**Methods:** From August 2014 to February 2017, patients with a large but resectable solitary HCC of >5 cm and a preoperative estimated resection margin of <1.0 cm were retrospectively studied. They were divided into one- and two-stage resection groups. A retrospective analysis was performed, followed by propensity score matching (PSM) analysis. Disease recurrence, survival, intraoperative and postoperative data were compared.

**Results:** Before PSM, the 1-, 2-, 3-and 4-year recurrence-free survival rates for the one- and two-stage groups were 44.3%, 31.7%, 24.3%, 19.2% versus 60.6%, 45.4%, 43.5%, 32.3%, respectively (P=0.007). The corresponding OS rates were 61.0%, 45.2%, 43.8%, 38.4% versus 69.6%, 62.5%, 60.7%, 57.3%, respectively (P=0.029). After PSM, the 1-, 2-, 3-and 4-year recurrence-free survival rates for the one- and two-stage groups were 44.0%, 31.5%, 27.3%, 21.0% versus 60.6%, 45.4%, 43.5%, 32.3%, respectively (P=0.013). The corresponding OS rates were 62.5%, 41.1%, 41.1%, 37.5% versus 69.6%, 62.5%, 60.7%, 57.3%, respectively (P=0.038). Differences in the resection margins between the one- and two-stage groups before [0.3 (0–0.5) versus 1.2 (0.8–2.2) cm] and after [0.2 (0–0.5) versus 1.2 (0.8–2.2) cm] PSM were also significant.

**Conclusions:** Two-stage hepatectomy allowed a wider resection margin for patients with a resectable but solitary HCC of >5 cm, and resulted in significantly better long-term survival outcomes after partial hepatectomy.

**Keywords:** One-stage hepatectomy; two-stage hepatectomy; large solitary hepatocellular carcinoma (HCC); resection margin

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Submitted Sep 15, 2020. Accepted for publication Dec 09, 2020.
doi: 10.21037/hbsn-20-711
**View this article at:** http://dx.doi.org/10.21037/hbsn-20-711

## Introduction

The only treatments which can offer a potential of cure for patients with hepatocellular carcinoma (HCC) are partial hepatectomy, liver transplantation and radiofrequency ablation (1-3). For patients with a large (>5 cm), solitary but resectable HCC, most liver centers consider liver transplantation (4) and radiofrequency ablation (s) not to be the treatment options for cure (5), and partial hepatectomy is the remaining choice (6,7). The Barcelona-Clinic Liver Cancer (BCLC) staging system recommends a solitary tumor with Child-Pugh of A-B to undergo liver resection (8,9).

The three-dimensional computed tomographic (3D-CT) visualization technology of liver for preoperative planning of liver resection has been used to determine resection margins and volumes of future liver remnants to allow adequate but safe partial hepatectomy (10-12). In a patient with a solitary and large HCC, the amount of liver tissues that needs to be resected can be large. In a background of liver fibrosis/cirrhosis, post-hepatectomy liver function can be compromised. To ensure a sufficient volume of future liver remnant (FLR), a one-stage hepatectomy may have to be carried out with a narrow resection margin. The alternative is to use a two-stage hepatectomy to allow hypertrophy of the non-tumorous liver to increase the resection margin. There is still no consensus on which treatment option is better.

In HCC, the width of surgical resection margin is a known and important factor affecting long-term survival outcomes after liver resection (13-17). However, there is still no international consensus on the optimal range of resection margins. In the commonly used international guidelines, margins of ≥0.5–1 cm have been recommended (13,18-20).

The commonly used 2-stage hepatectomy to promote compensatory increase in FLR for patients with unresectable HCC include portal vein embolization (PVE), and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) (21-23).

The role of two-stage hepatectomy in patients who undergo one-stage hepatectomy with possibility of only achieving narrow resection margins has not been studied. The aim of the study was to compare the long-term survival outcomes of these patients who underwent one- or two-stage major hepatectomy and who were assessed preoperatively to have narrow resection margins for a solitary but large HCC of >5 cm in diameter.

## Methods

### *Patients*

This is a retrospective, single-center study. From August 2014 to February 2017, consecutive patients who underwent major partial hepatectomy (resection of >3 Couinaud liver segments) for a large but resectable solitary HCC of >5 cm in diameter and who were assessed by preoperative 3D-CT visualization to have adequate volumes of FLR but narrow resection margins of <1.0 cm entered into this study. It is known that a preoperatively planned width of resection margin might not be achieved on postoperative histopathological study of resected specimens. A detailed discussion was made between the operating surgeon and the patient to decide on the one- or two-stage approach for partial hepatectomy, resulting in two groups of patients in this study: the one-stage hepatectomy group, and the two-stage hepatectomy group. When patients decided to undergo a two-stage operation, further discussion was made on the merits and demerits of PVE versus ALPPS. The final decision was made with a consensus in opinions reached between the patient and the surgeon. The diagnosis of HCC and the determination of the actual resection margins were based on postoperative histopathological studies. The study was censored on May 31, 2019 and the follow-up periods for all the patients were >24 months, with a median follow-up of 36 months. All the operations were carried out with curative intent.

### *Inclusion and exclusion criteria*

The inclusion criteria were patients: (I) aged 18–75 years, (II) who underwent 3D-CT visualization before surgery, with preoperative planning performed by a three-dimensional visualization software, (III) who had a FLR volume which met the following requirements [FLR/standard liver volume (SLV) >30% in normal livers or ≥40% in cirrhosis], (IV) with an estimated preoperative resection

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margin <1.0 cm.

Cirrhosis was diagnosed based on any one of the following findings: (I) ultrasonic or other imaging examinations showing liver shrinkage, uneven surface, blunt liver edges, uneven liver parenchyma, and nodular shapes, (II) gastric/esophageal varices, (III) an inner diameter of portal vein greater than 13 mm and/or inner diameter of splenic vein greater than 8 mm, (IV) thickness of splenic hilum greater than 4 cm. The exclusion criteria were: (I) patients who refused to participate in this clinical trial, (II) hepatic dysfunction with a Child-Pugh score of Grade B or C, (III) portal hypertension, ascites, or any other serious extrahepatic complications of cirrhosis. We present the following article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-711/rc).

## Methods

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was reviewed and approved by the Ethics Committee of Eastern Hepatobiliary Surgery Hospital. The Ethics Number is EHBHKY2014-03-019. All patients enrolled in this study signed an informed consent. This study was registered with the Chinese Clinical Trials Registry (ChiCTR) website and the Registration Number was ChiCTR-IOC-14005646.

### *Propensity score matching (PSM)*

A propensity score was used to match the two groups of patients based on the results of the retrospective analysis to eliminate the impact of baseline differences on patient prognosis. The matched items included: main tumor diameter, microvascular invasion (MVI), age, gender, degree of liver fibrosis, and HBV-DNA levels. The matching was performed in a 1:1 ratio with a match tolerance of 0.1.

### *Three-dimensional visualization surgery planning and FLR calculation*

All patients underwent abdominal intravenous contrast enhanced CT scan using a GE 64-slice CT scanner before surgery with a layer thickness of 1.25 mm. The data was stored in Digital Imaging and Communications in Medicine (DICOM) format. Either EDDA's IQQA or Shenzhen Xudong's three-dimensional visualization software was used for three-dimensional reconstruction and preoperative surgical planning. With participation of the operating surgeons and software technicians, resection was simulated according to the surgical plan, and the residual liver volume was calculated. The SLV calculation formula is: SLV (mL) = 706.2 × BSA ($m^2$) + 2.4 (24).

### *Surgical margin and histological determination*

The surgical resection margin was defined as the minimum distance of normal liver parenchyma from the edge of tumor. Postoperative margins were obtained from experienced pathologists after surgery. The margin of preoperative planning was performed by surgeons and software technicians using the three-dimensional visualization computer software. R0 resection was defined as no residual tumor cells on histological examination of the liver resection edge. R1 resection was defined as presence of tumor cells on histological examination of the resection edge.

### *Study design*

ALPPS was carried out using open surgery in the way as previously reported (25). PVE was conducted using embolization with Gelfoam particles with or without coils. The operative procedure was performed following the methods as previously reported (26). In brief, the process is as follows: the patient was placed in the supine position, anesthetized and disinfected, and a L-shaped incision of the abdomen was performed. A ultrasonic dissector was used to gradually transect the tumor-bearing liver from the remnant liver along a preoperatively planned plane. If necessary, surgical bleeding was controlled, and hepatic portal blood flow was blocked by Pringle's maneuver. The wound was cleaned after the tumor was removed, and the abdomen was closed. Transcatheter arterial chemoembolization (TACE) was conducted before PVE due to the long waiting time for liver enlargement to reach to adequate volumes of FLR after PVE. PVE was then carried out 2 weeks later when the liver function had returned to normal. During the waiting period, TACE was performed once every 4 weeks to control tumor growth. Sequential TACE and PVE is an established technique (27,28). The use of Gelfoam particles to embolize part of the portal venous system allows recanalization and TACE to be repeated in patients with inadequate hypertrophy of FLR, followed by permanent embolization using coils (29). CT was performed once every week after the first stage of surgery. If the requirements of the margin

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of >1.0 cm was met, surgical resection was performed, and if the requirement was not met, then CT scan was performed until the margin met the requirement, or until treatment failure occurred.

Treatment failure was defined as tumor progression resulting in unresectability, multiple intrahepatic or distant metastases of liver tumors, inadequate rate of enlargement of liver of less than 2% in a week, serious treatment complications or death.

### *Study endpoints*

The primary end-points were overall survival (OS) and recurrence-free survival. Both OS and recurrence-free survival were counted from the day of surgical resection. Secondary end-points were intraoperative data and postoperative complications.

### *Statistical analysis*

A propensity score for the two groups of patients was used to perform a 1:1 matching ratio with a tolerance of 0.1. The matched items included: main tumor diameter, MVI, age, gender, degree of liver fibrosis, and HBV-DNA levels.

Continuous variables were expressed as median and range, and compared by the Mann-Whitney U test. Categorical variables were expressed as numbers and ratios, and compared by the Chi-squared test or Fisher's exact test. OS was calculated from the date of liver resection until death or the last date of follow-up. Recurrence-free survival was calculated from the date of liver resection until the first HCC recurrence. OS and recurrence-free survival outcomes were calculated using the Kaplan-Meier method and compared using the Log-rank method. Univariate and multivariate analyses were performed using the Cox regression model with stepwise selection of variables. A P<0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Program for Social Sciences (SPSS 23.0 for Windows).

## Results

### *Comparison of baseline data and surgical margins in patients before matching*

During the study period, of 2,256 patients who underwent hepatectomy in our center, 202 patients satisfied the inclusion and exclusion criteria and were included into this study. There were 146 patients in the one-stage and 56 patients in the two-stage hepatectomy groups (ALPPS =34 and PVE =22). There were no significant differences between the baseline data of these two groups except in the resection margin: 0.3 (0–0.5) cm for the one-stage and 1.2 (0.8–2.2) cm for the two-stage hepatectomy groups (P<0.001), and in the resection type (P=0.008; *Table 1*). There were 17 patients with R1 resection, and they were all in the one-stage hepatectomy group. The 1-, 2-, 3-, and 4-year recurrence-free survival rates of R0 resection patients were 53.4%, 38.9%, 32.7%, and 25.6%, respectively. All R1 resection patients relapsed within one year of surgery, and 41.2% of patients relapsed within 6 months. The 1-, 2-, 3-, and 4-year OS for patients with R0 and R1 resections were 67.0%, 54.1%, 52.4%, 45.9% versus 17.6%, 5.9%, 5.9%, 5.9%, respectively (P<0.001). R1 resection resulted in significantly lower recurrence-free survival and OS outcomes. A preoperative planned wide surgical margin resulted in a significantly higher R0 resection rate.

The 1-, 2-, 3-, and 4-year recurrence-free survival rates in the one-stage and the two-stage hepatectomy groups were 44.3%, 31.7%, 24.3%, 19.2% versus 60.6%, 45.4%, 43.5%,32.3%, respectively (P=0.007; *Figure 1*).

The corresponding OS rates for the two groups were 61.0%, 45.2%, 43.8%, 38.4% versus 69.6%, 62.5%, 60.7%, 57.3%, respectively. The difference was again significant (P=0.029; *Figure 1*).

The operation time, duration of hepatic vascular occlusion, and units of blood cell transfusion were significantly higher, but the amount of intraoperative bleeding were similar, and major postoperative complications (≥IIIa) were significantly lower in the one-stage than the two-stage hepatectomy groups (*Table 2*). There were no significant differences in postoperative overall complications, post hepatectomy liver failure (PHLF), and postoperative 90-day mortality between the two groups (*Table 3*).

### *Univariate and multivariate regression analyses of survival and recurrence*

Univariate analysis by the Cox regression model on age, gender, treatment grouping, main tumor diameter, MVI (+), HBV-DNA (>50 IU/mL), HBsAg (+), resection margin, resection type (R1), degree of liver fibrosis, and alpha-fetoprotein (>20 μg/L) showed treatment grouping, main tumor diameter, MVI (+), HBV-DNA (>50 IU/mL), resection margin, R1 resection and degree of liver fibrosis to be significant factors for HCC recurrence. Treatment grouping,

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**Table 1** Baseline characteristics of patients

| Parameters | Before matching with PS | | | After matching with PS | | |
|---|---|---|---|---|---|---|
| | One-stage hepatectomy (n=146) | Two-stage hepatectomy (n=56) | P | One-stage hepatectomy (n=56) | Two-stage hepatectomy (n=56) | P |
| Age, yrs [range] | 50 [25–77] | 49 [27–72] | 0.869 | 49 [25–70] | 49 [27–72] | 0.411 |
| Gender, male, n (%) | 120 (82.19) | 49 (87.50) | 0.483 | 49 (87.50) | 49 (87.50) | 0.612 |
| Main tumor diameter (cm) | 9.45 (5.0–24.40) | 9.33 (5.0–16.82) | 0.395 | 9.50 (5.0–24.40) | 9.33 (5.0–16.82) | 0.629 |
| MVI, n (%) | | | | | | |
| Positive | 79 (54.11) | 24 (42.86) | 0.202 | 29 (51.79) | 24 (42.86) | 0.225 |
| Negative | 67 (45.89) | 32 (57.14) | | 27 (48.21) | 32 (57.14) | |
| Platelet count, ($10^9$/L) | 183 (51–494) | 160 (65–369) | 0.205 | 187.5 (72–332) | 160 (65–369) | 0.159 |
| HBV-DNA >50 (IU/mL), n (%) | 59 (40.41) | 29 (51.79) | 0.193 | 27 (48.21) | 29 (51.79) | 0.425 |
| AFP >20 μg/L, n (%) | 75 (51.37) | 35 (62.50) | 0.206 | 30 (53.57) | 35 (62.50) | 0.222 |
| HBsAg+, n (%) | 136 (93.15) | 48 (85.71) | 0.166 | 50 (89.29) | 48 (85.71) | 0.388 |
| TB (μmol/L) | 15.15 (4.5–203.3) | 13.55 (6–31) | 0.156 | 13.4 (4.5–61.1) | 13.55 (6–31.0) | 0.619 |
| ALB (U/L) | 37.85 (34.1–48.8) | 41.2 (33.6–51.3) | 0.432 | 37.55 (34.1–47.9) | 41.2 (33.6–51.3) | 0.451 |
| INR (s) | 0.96 (0.84–1.12) | 0.99 (0.82–1.15) | 0.331 | 0.98 (0.84–1.11) | 0.99 (0.82–1.15) | 0.362 |
| Surgical margin (cm) | 0.3 (0–0.5) | 1.2 (0.8–2.2) | <0.001 | 0.2 (0–0.5) | 1.2 (0.8–2.2) | <0.001 |
| Resection type, n (%) | | | 0.008 | | | 0.022 |
| R0 resection | 129 (88.36) | 56 (100.00) | | 51 (91.07) | 56 (100.00) | |
| R1 resection | 17 (11.64) | 0 | | 5 (8.93) | 0 | |
| Liver fibrosis ≥3, n (%) | 113 (77.39) | 45 (80.36) | 0.648 | 45 (80.36) | 45 (80.36) | 1 |
| Child-Pugh score, n (%) | | | | | | |
| A | 146 (100.00) | 56 (100.00) | 1 | 56 (100.00) | 56 (100.00) | 1 |
| B | 0 | 0 | | | 0 | |
| C | 0 | 0 | | | 0 | |
| BCLC stage (%) | | | | | | |
| 0 | 0 | 0 | 1 | 0 | 0 | |
| A | 146 (100.00) | 56 (100.00) | | 56 (100.00) | 56 (100.00) | |
| B | 0 | 0 | | 0 | 0 | |

PS, propensity score; MVI, microvascular invasion; AFP, alpha-fetoprotein; HBsAg, hepatitis B surface antigen; TB, total bilirubin; ALB, albumin; INR, international normalized ratio; BCLC, Barcelona Clinic Liver Cancer classification.

main tumor diameter, MVI, HBV-DNA (>50 IU/mL), resection margin, resection type (R1), degree of liver fibrosis, and alpha-fetoprotein (>20 μg/L) were significant factors for overall survival (*Table 4*).

Multivariate analysis showed resection margin, resection type (R1), main tumor diameter, and MVI to be significant risk factors for HCC recurrence. Resection margin, MVI, and HBV-DNA (>50 IU/mL) were significant risk factors for OS. Thus, surgical margin was both a significant factor for HCC recurrence and overall survival (P=0.001, HR

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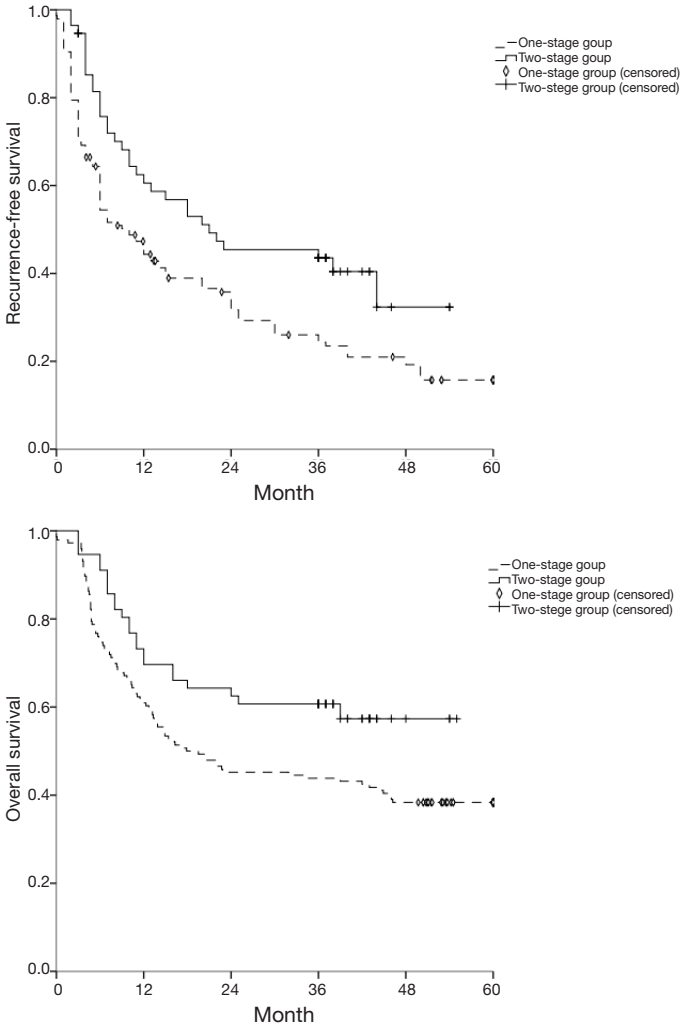


**Figure 1** Comparison of recurrence-free survivals and overall survival between the 2 groups before matching (P=0.007 and 0.029, respectively, log-rank).

=0.489, 95% CI: 0.323–0.739; P=0.002, HR =0.455, 95% CI: 0.275–0.755; *Table 5*). As treatment grouping was not a risk factor for both HCC recurrence and overall survival, its impact on long-term survival outcomes was mainly caused by the difference in resection margins between the two groups.

### *Comparison of intraoperative data and postoperative complications between ALPPS and PVE*

The results of intraoperative and postoperative data of ALPPS and PVE in the two-stage hepatectomy group were compared. The results showed that the operation time and hepatic vascular occlusion time in the ALPPS group were significantly less, transfusion of blood cell units and intraoperative bleeding were similar, and incidence of major postoperative complications (≥IIIa) was significantly higher than the PVE group (17 *vs.* 4). As the ALPPS patients were involved in two operative procedures, the baseline operation time of the second-stage hepatectomy was significantly less, but major complications were significantly more than one-stage hepatectomy (*Table 2*).

### *Comparison of baseline data and resection margins in patients after PSM*

After PSM, there were 56 patients in each of the two groups

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**Table 2** Comparison of intraoperative and postoperative data between ALPPS and PVE

| Parameters | ALPPS (n=34) | PVE (n=22) | P |
|---|---|---|---|
| Liver hypertrophy time [days] | 12 [7–28] | 43 [28–56] | <0.001 |
| Operation time (min) | 142.5 (105–270) | 210 (140–270) | <0.001 |
| Pringle maneuver duration (min) | 11.5 (0–22.0) | 21.0 (0–44.0) | <0.001 |
| Number of blood transfusion, n (%) | 16 (47.06) | 12 (54.55) | 0.584 |
| Bleeding volume (mL) | 400 (50–4,700) | 800 (200–4,400) | 0.194 |
| Type of hepatectomy, n (%) | | | |
| Right hepatectomy | 20 (58.82) | 16 (72.73) | |
| Left hepatectomy | 2 (5.88) | 0 | |
| Right trisectionectomy | 8 (23.53) | 6 (27.27) | |
| Left trisectionectomy | 4 (11.76) | 0 | |
| Postoperative complications, n (%) | 32 (94.12) | 19 (86.36) | 0.607 |
| Major complications (≥IIIa), n (%) | 17 (50.00) | 4 (18.18) | 0.034 |
| Bile leakage + ascites + pleural effusion | 1 | 0 | |
| Bile leakage + ascites | 1 | 0 | |
| Atelectasis + intra-abdominal infection | 1 | 0 | |
| Pleural effusion + hemorrhage | 3 | 0 | |
| Pleural effusion + disruption of wound | 2 | 0 | |
| Pleural effusion | 4 | 0 | |
| Hemorrhage | 2 | 2 | |
| Ascites | 1 | 1 | |
| Bile leakage | 2 | 1 | |
| Severe complications (≥IIIb), n (%) | 7 (20.59) | 3 (13.64) | 0.759 |
| Postoperative liver failure | 0 | 0 | |
| 90-day mortality, n (%) | 2 (5.88) | 3 (13.64) | 0.607 |
| Tumor progression | 0 | 1 (4.55) | |
| Hepatic dysfunction | 2 (5.88) | 2 (9.09) | |

ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; PVE, portal vein embolization.

of patients. There were no significant differences in the preoperative baseline data between the two groups (*Table 1*).

In the one-stage hepatectomy group, of 33 (58.9%) patients who relapsed within 1 year, 20 (35.7%) relapsed within 3 months. In the two-stage hepatectomy group, of 24 (42.9%) patients who relapsed within one year, 6 (10.7%) relapsed within 3 months. The median recurrence was 8 months in the one-stage hepatectomy group and 21 months in the two-stage hepatectomy group. After PSM, the recurrence-free survival rates of 1-, 2-, 3-, and 4-years in the one-stage hepatectomy group were 44.0%, 31.5%, 27.3%, and 21.0% versus the two-stage hepatectomy group of 60.6%, 45.4%, 43.5%, and 32.3%. The recurrence-free survival rates of the two-stage hepatectomy were significantly better than that of the one-stage hepatectomy group (*Figure 2*).

There were 23 (41.1%) patients who survived for more than 3 years in the one-stage hepatecomy group and

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**Table 3** Intraoperative and postoperative data of patients in the two groups

| Parameters | Before matching with PS | | | After matching with PS | | |
|---|---|---|---|---|---|---|
| | One-stage hepatectomy (n=146) | Two-stage hepatectomy (n=56) | P | One-stage hepatectomy (n=56) | Two-stage hepatectomy (n=56) | P |
| Operation time (min) | 250 (185–370) | 165 (105–270) | <0.001 | 250 (200–370) | 165 (105–270) | <0.001 |
| Pringle maneuver duration (min) | 32.0 (0–66.0) | 15.5 (0–44.0) | <0.001 | 30.0 (0–66.0) | 15.5 (0–44.0) | <0.001 |
| Number of blood transfusion, n (%) | 91 (62.33) | 28 (50.0) | 0.111 | 36 (64.29) | 28 (50.0) | 0.127 |
| Bleeding volume (mL) | 500 (200–2,000) | 550 (50–4,700) | 0.520 | 500 (200–1,200) | 550 (50–4,700) | 0.484 |
| Type of hepatectomy, n (%) | | | | | | |
| Right hepatectomy | 33 (22.60) | 36 (64.29) | | 19 (33.93) | 36 (64.29) | |
| Left hepatectomy | 15 (10.27) | 2 (3.57) | | 2 (3.57) | 2 (3.57) | |
| Right trisectionectomy | 10 (6.85) | 14 (25.00) | | 6 (10.71) | 14 (25.00) | |
| Left trisectionectomy | 2 (1.37) | 4 (7.14) | | 0 (0.00) | 4 (7.14) | |
| Local resection | 86 (58.90) | 0 (0.00) | | 29 (51.79) | 0 (0.00) | |
| Postoperative complications, n (%) | 130 (89.04) | 50 (89.29) | 0.591 | 49 (87.50) | 51 (91.07) | 0.760 |
| Major complications (≥IIIa), n (%) | 30 (20.55) | 21 (37.50) | 0.012 | 11 (19.64) | 21 (37.50) | 0.029 |
| Severe complications (≥IIIb), n (%) | 22 (15.07) | 10 (17.86) | 0.386 | 8 (14.29) | 10 (17.86) | 0.399 |
| Postoperative liver failure | 0 | 0 | 1 | 0 | 0 | 1 |
| 90-day mortality, n (%) | 4 (2.74) | 5 (8.93) | 0.127 | 4 (7.14) | 5 (8.93) | 1 |

PS, propensity score.

34 (60.7%) in the two-stage hepatectomy group. After PSM, the 1-, 2-, 3-, and 4-year OS rates for the one-stage hepatectomy group were: 62.5%, 41.1%, 41.1%, and 37.5% compared with the two-stage hepatectomy group of 69.6%, 62.5%, 60.7%, and 57.3%. The OS rates of the two-stage hepatectomy were significantly better than the one-stage hepatectomy group (*Figure 2*).

There was significant difference in the width of resection margins between the two groups (P<0.01). The surgical margin (cm) in the two-stage hepatectomy group was significantly greater than that of the one-stage hepatectomy, being 1.2 (0.8–2.2) and 0.3 (0–0.5) cm, respectively. The resection margins of the two-stage resection group were all ≥0.8 cm, both before and after PSM (*Table 1*). However, for the one-stage hepatectomy group, the resection margins in some patients, both before and after PSM, could be as low as 0 cm (R1 resection).

### *Comparison of intraoperative data and postoperative complications in patients after PSM*

After PSM, the operation time and vascular hepatic occlusion time of the one-stage hepatectomy group were significantly longer, while intraoperative bleeding, postoperative overall complications (49 *vs.* 51), severe complications (8 *vs.* 10), postoperative liver failure (0 *vs.* 0), and postoperative 90-day mortality (4 *vs.* 5) were similar, but the preoperative major complication rate (≥IIIa) was significantly less than the two-stage hepatectomy group (11 *vs.* 21, P=0.029; *Table 3*).

## Discussion

Two-stage hepatectomy has mainly been used in patients with unresectable liver cancer due to insufficient volumes of FLR to increase the resection rate. Whether the use of

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**Table 4** Univariate regression analysis of recurrence and survival

| Factors | Recurrence | | OS | |
|---|---|---|---|---|
| | HR (95% CI) | P | HR (95% CI) | P |
| Age | 1.001 (0.985–1.018) | 0.899 | 0.995 (0.977–1.014) | 0.621 |
| Gender, male | 1.244 (0.784–1.976) | 0.354 | 1.043 (0.637–1.707) | 0.868 |
| Group (1= one-stage) | 0.592 (0.399–0.878) | 0.009 | 0.603 (0.614–0.955) | 0.031 |
| Main tumor diameter | 1.080 (1.045–1.116) | <0.001 | 1.081 (1.040–1.123) | <0.001 |
| MVI (+) | 5.405 (3.704–7.874) | <0.001 | 7.042 (4.464–10.989) | <0.001 |
| HBV-DNA >50 (IU/mL) | 1.727 (1.247–2.392) | 0.001 | 1.992 (1.374–2.890) | <0.001 |
| Surgical margin | 0.547 (0.372–0.805) | 0.002 | 0.508 (0.314–0.819) | 0.006 |
| Resection type (R1) | 4.469 (2.583–7.730) | <0.001 | 3.253 (1.887–5.609) | <0.001 |
| Fibrosis level ≥3 | 1.672 (1.206–2.315) | 0.002 | 1.675 (1.159–2.427) | 0.006 |
| AFP >20 μg/L | 1.269 (0.915–1.761) | 0.153 | 1.567 (1.072–2.294) | 0.020 |

OS, overall survival; MVI, microvascular invasion; AFP, alpha-fetoprotein.

**Table 5** Multivariate regression analysis of recurrence and survival

| Factors | Recurrence | | OS | |
|---|---|---|---|---|
| | HR (95% CI) | P | HR (95% CI) | P |
| Surgical margin | 0.489 (0.323–0.739) | 0.001 | 0.455 (0.275–0.755) | 0.002 |
| Resection type (R1) | 2.473 (1.413–4.327) | 0.002 | | |
| Main tumor diameter | 1.052 (1.013–1.093) | 0.009 | | |
| MVI (+) | 6.028 (3.955–9.187) | 0.001 | 6.711 (4.255–10.638) | 0.001 |
| HBV-DNA >50 (IU/mL) | | | 1.493 (1.022–2.179) | 0.038 |

OS, overall survival; MVI, microvascular invasion.

two-stage hepatectomy to allow a more adequate resection margin is more beneficial than a one-stage hepatectomy has not been reported. Our study suggested that a wider surgical margin is important in influencing long-term survival outcomes in patients with a solitary HCC of >5 cm in diameter.

The resection margin in liver resection refers to the minimum distance of tumor from non-tumorous tissues. Liver resection can be divided into R0, R1, and R2 resections. However, there is currently no consensus on how much this distance needs to be to differentiate between R0 and R1 resections. Our research shows that the R0 resection rate (100%) of the two-stage hepatectomy group after extending the resection margin was higher than the one-stage hepatectomy group (88.36%). At the same time, patients with R0 resection had better recurrence-free survival and OS than those with R1 resection. In major liver resection, a balance between safety and surgical margin is important. While it is necessary to conserve as much functioning liver parenchyma as possible, an adequate resection margin to achieve R0 resection is also important. Even when histopathology shows R0 resection, recurrence of HCC has been shown to associate with micrometastasis which can be present outside of the resection margin if the resected marginal width is too narrow. The width of resection margin for HCC is still controversial (18). Previous studies and guidelines recommend a resection margin which varies from 0.5 to 2 cm (24-26,30,31). These studies and guidelines, however, all agree that an adequate resection margin to achieve R0 resection is important in reducing recurrence and prolonging long-term survival outcomes of patients. Our study showed that in patients

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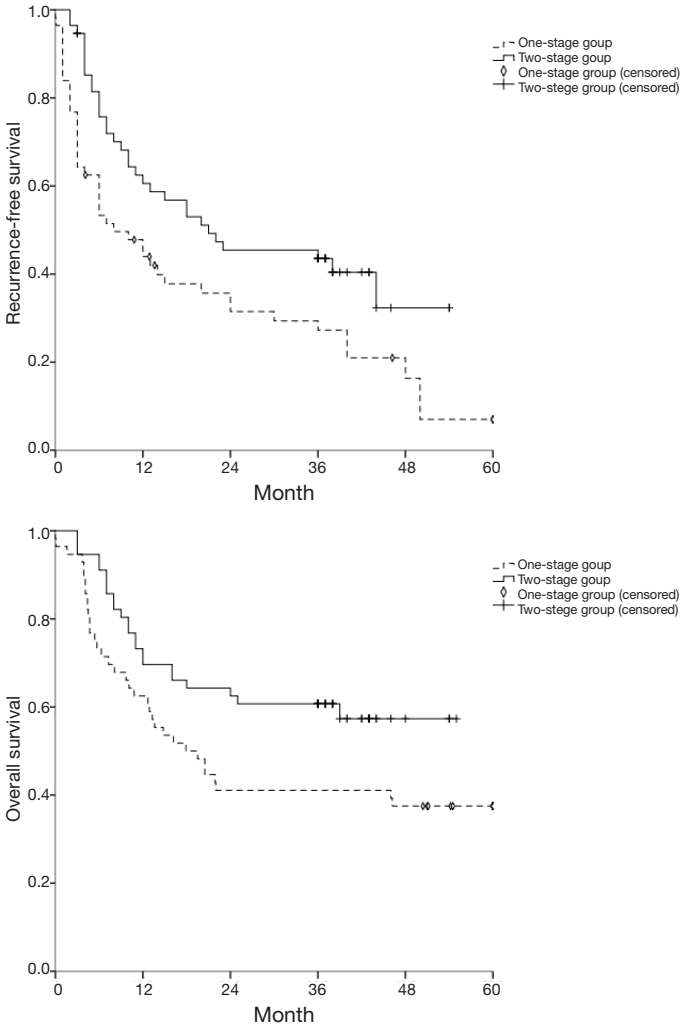


**Figure 2** Comparison of recurrence-free survivals and overall survival between the 2 groups after matching (P=0.013 and 0.038, respectively, log-rank).

who were assessed preoperatively to have a narrow resection margin, two-stage hepatectomy could improve the resection margin with resultant improvement in recurrence-free and OS outcomes.

To enable adequate volumes of FLR after major hepatectomy, two-stage hepatectomy using PVE or ALPPS has been commonly used. PVE blocks the portal venous blood flow to the part of the liver containing the tumor, resulting in compensatory hyperplasia of the remaining liver. This was first used by Makuuchi in the treatment of intrahepatic cholangiocarcinoma (32). On the other hand, ALPPS is performed by two stages of surgery. In surgery stage I, the portal supply to the part of liver to be resected is disconnected and the plane between the parts of the liver to be resected or preserved is made. In surgery stage II, surgical resection is performed after adequate hyperplasia of FLR. ALPPS can rapidly increase the volume of FLR (33-35). Further developments in two-stage hepatectomy include the use of PVE combined with TACE to decrease tumor growth during the waiting time for increase in volume of FLR (36). Advances in PVE materials to improve regeneration speed of FLR and improvement in surgical experience result in decline of postoperative complications of ALPPS (30-33). In our study, the increased volumes of FLR allowed wider resection margins in the 2-stage hepatectomy.

Three-dimensional visualization technology allows surgeons to simulate surgical resection in preoperative surgical planning, to accurately calculate volumes of FLR,

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and to predetermine and assess resection margins. This technology has been shown to improve safety of surgery and it is useful in surgical planning (10). In this study, three-dimensional visualization technology allowed us to determine liver regeneration in two-stage hepatectomy, and to extend resection margins, thus finally improving the R0 surgical resection rate, reduced postoperative liver failure, and improved long-term survival outcomes of patients.

The limitations of this study are: first, this is a retrospective study with its inherent defects. Second, this study did not use current advances in PVE materials, such as NBCA and microspheres (34-36) which can result in faster liver hyperplasia rates. Third, this is a single center study. The results may not be applied in other centers. Fourth, this study was designed as a retrospective study which aimed to compare long-term survival outcomes in patients who underwent one- or two-stage major hepatectomy and who were assessed preoperatively to have narrow resection margins for a solitary but large HCC >5 cm in diameter. This study was not designed to study treatment failure, disease progression in between stages for two-stage hepatectomy and it was not based on intention-to-treat analysis. As a consequence, biases can be introduced and further prospective studies need to be conducted to clarify these points.

In conclusion, this study suggested that resection margins affected recurrence and prognosis of patients with a solitary HCC of >5 cm in diameter after major hepatectomy. Two-stage hepatectomy extended the resection margins in these patients. Preoperative three-dimensional visualization reconstruction and surgical simulation were important in determining volumes of FLR and surgical resection margins.

## Acknowledgments

*Funding:* This study was supported by: Science Fund for Creative Research Groups, NSFC, China (81521091); State Key Infection Disease Project of China (2018ZX10732202-002-005); Shanghai Rising Star Program (20QA1412000); National Natural Science Foundation of China (81702734); Natural Science Foundation of Shanghai Municipal Commission of Health and Family Planning (Y20170006, 2017Y0109).

## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-711/rc

*Data Sharing Statement:* Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-711/dss

*Conflicts of Interest*: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-20-711/coif). WYL serves as an unpaid editorial board member of *Hepatobiliary Surgery and Nutrition*. The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was reviewed and approved by the Ethics Committee of Eastern Hepatobiliary Surgery Hospital. The Ethics Number is EHBHKY2014-03-019. All patients enrolled in this study signed an informed consent. This study was registered with the Chinese Clinical Trials Registry (ChiCTR) website and the Registration Number was ChiCTR-IOC-14005646.

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**Cite this article as:** Li Y, Li PP, Sun DP, Ni JS, Liu H, Pan ZY, Yang Y, Zhao LH, Lau WY, Huang G, Zhou WP. One- versus two-stage partial hepatectomy for large resectable solitary hepatocellular carcinomas determined preoperatively to have a narrow resection margin: a propensity score matching analysis. HepatoBiliary Surg Nutr 2022;11(5):662-674. doi: 10.21037/hbsn-20-711

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