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Modified Procedures for ALPPS Based on a Risk-Reduced Strategy: Paralleled Clinical Evaluation at Multiple Institutions

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Purpose: We compared the clinical outcomes of modified procedures for associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) based on a risk-reduced strategy with those of classic ALPPS procedures in treating large liver carcinoma.

Materials and Methods: Short-term outcomes, increases in future liver remnant (FLR) and functional FLR (FFLR), and overall survival (OS) were compared between 45 consecutive patients treated with modified ALPPS procedures and 34 patients treated with classic ALPPS procedures.

Results: Clinical outcomes after the 1st-stage operation markedly improved with the modified procedures. Although the proportions of liver cirrhosis and hepatocellular carcinoma were higher in the modified group, the mortality and incidence of severe complications did not increase. FLR and FFLR hypertrophy at 1 week after the 1st-stage operation were similar in both groups; however, kinetic growth rates in the modified group were lower. OS rates were similar.

Conclusion: Modified ALPPS procedures could be safely applied to provide long-term survival for patients with liver cirrhosis without sufficient FLR.

Key Words: ALPPS, liver carcinoma, liver cirrhosis, complication, survival

INTRODUCTION

Radical resection remains the only potential curative treatment for liver tumors, whether primary or metastatic. However, due to insufficient future liver remnant (FLR) volume, which often occurs in hepatocellular carcinoma (HCC) with obvious liver cirrhosis or in metastatic liver tumors with multiple lobes involved, only 30% of patients benefit from radical hepatectomy.[1] Thus, most patients must turn to palliative treatments, such as radiofrequency/microwave ablation (RFA/MWA), transcatheter arterial chemoembolization (TACE), and immunotherapy or targeted drug therapy. Meanwhile, anticipated postoperative liver failure accounts for 60%–70% of unresectable liver tumors.[2,3]

As a new 2-stage hepatectomy approach, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been applied to induce an accelerated FLR growth of 40%–160% within 6–9 days, while avoiding tumor progression and troublesome adhesions. Research has shown ALPPS to be successful in 70%–80% of patients otherwise likely to

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have a poor prognosis.[4] However, tremendous controversy, due to a high reported mortality (up to 25%) and morbidity (up to 40%), confounds the use of ALPSS, so much so that some hepatobiliary surgeons have abandon it after initial attempts.[5] Accordingly, reaching a balance between rapid increases in functional FLR (FFLR) and the trauma incurred by consecutive operations in a short period of time has been the focus of ALPPS research.

Building on our experiences with ALPPS, we formulated and applied a series of modified procedures based on a risk-reduced strategy to reach the balance between rapid FFLR increases and trauma reduction. This strategy included meticulous risk evaluation in patient selection, accurate assessment of FLR and FFLR, precise operation planning, and techniques for non-transection of the liver. In this article, we sought to systematically evaluate the feasibility and efficacy of these modified ALPPS procedures via paralleled comparison among multiple institutions.

MATERIALS AND METHODS

This study reviewed all patients who underwent modified ALPPS procedures at Chinese PLA Air Force Medical Center, Beijing Tiantan Hospital Affiliated to Capital Medical University, and Zibo Central Hospital from January 2016 to December 2020. All patients were diagnosed according to clinical features, laboratory tests, and imaging findings, and diagnoses were confirmed by pathological results. All patients had been referred for treatment of liver carcinoma, including liver transplantation, hepatectomy, RFA/MWA, TACE, and immunotherapy or targeted drug therapy, etc. Each patient made the final choice on the treatment option after being well informed of the potential risks of ALPPS and signed informed consent. For comparison, we analyzed the data of patients who were treated with classic ALPPS procedures between January 2012 and February 2017. Details on the operation, complications, short-term outcomes, sequential changes on FLR and FFLR volume assessed by 64-slice multidetector computed tomography (MDCT) and single-photon emission computed tomography (SPECT), and overall survival (OS) were compared. This multiple-institution study was conducted in compliance with the Declaration of Helsinki (Fortaleza, Brazil, October 2013). The Ethics Committee of the Chinese PLA Air Force Medical Center approved this study (No.2017AGA-024).

Patient selection

Candidates for ALPPS were limited to those with primary or metastatic liver carcinoma. Patients with gallbladder carcinoma or hilar cholangiocarcinoma were excluded because of dilation of the intrahepatic bile duct. For initial risk evaluation, the Child-Pugh-Turcotte (CPT) and the Model of End-Stage Liver Disease (MELD) scoring systems were used to assess liver function. Patients with a CPT score of C or MELD scores above 24 were excluded. Next, the Albumin-Indocyanine Green Evaluation (ALICE) grading system was applied for further risk evaluation.[6] Patients with an ALICE grade of 3 (linear predictor value of less than -1.39) were also excluded. The criteria for FLR (calculation of FLR is presented in the next section) were as follows: 1) FLR/standardized liver volume (SLV) <25% or FLR/body weight (BW) <0.5% in patients with CPT A, MELD <9, and ALICE grade 1; 2) FLR/SLV <30% in patients of ALICE grade 2a or CPT A; 3) FLR/SLV <40% or FLR/BW <0.8% in patients of CPT A or ALICE grade 2a, with MELD scores of 9–15; and 4) FLR/SLV <50% in patients of CPT B or ALICE grade 2b, with MELD scores of 16–24. Patients were excluded from ALPPS if they presented with 1) unresectable liver cancer on FLR; 2) unresectable extrahepatic tumor; 3) liver cirrhosis with severe portal hypertension; 4) unavailable R0 margin on the liver; or 5) inability to undergo anesthesia or surgery. Postoperative complications were defined according to the Clavien–Dindo classification, and severe complications were defined as ≥grade IIIb.[7]

FLR assessment and surgical planning

In the modified ALPPS group, FLR-related data were obtained from MDCT and three-dimensional (3D) imaging reconstruction. The 64-slice MDCT parameters were set at a slice thickness of 1.25 mm, a scanning time per rotation of 0.6 s, a table speed of 13.5 mm/rotation, and a reconstruction interval of 2 mm. A compound meglumine diatrizoate injection was infused at 3.5 mL/s for enhanced scanning, with images obtained at 5 s in the arterial phase, 20 s in the portal phase, and 70 s in the venous phase after arriving at peak aortic enhancement. After MDCT scanning, all images were collected and analyzed using 3D image processing software (Myrain-XP liver, Paris, France). Sequentially, all images related to hepatic carcinoma were extracted, reconstructed, overlapped, and integrated into 3D images through region-growing or level-set techniques. Transparent and rotatable views of the liver with surrounding vessels, as well as characteristics of the tumor, could be obtained, after which FLR could be calculated based on simulated hepatectomy (Fig. 1). In the classic ALPPS group, only MDCT was used to designate liver anatomy and to calculate FLR using Couinaud's classification. Body surface area (BSA) was calculated using Stevenson's formula: BSA (m^2)=0.0061×body height (cm) +0.0128×BW (kg). SLV was calculated according to Urata's formula: SLV (mL)=706.2×BSA+2.4. From these, FLR/SLV and FLR/BW were calculated, applying cutoff values known to be correlated with adverse outcomes.[8]

ALPPS procedures

In the modified group, the 1st-stage operation was performed by non-transection of the liver, assisted by laparoscopic RFA. The right hepatic artery, right portal vein, and right bile duct were dissected separately in Glisson's sheath near the porta

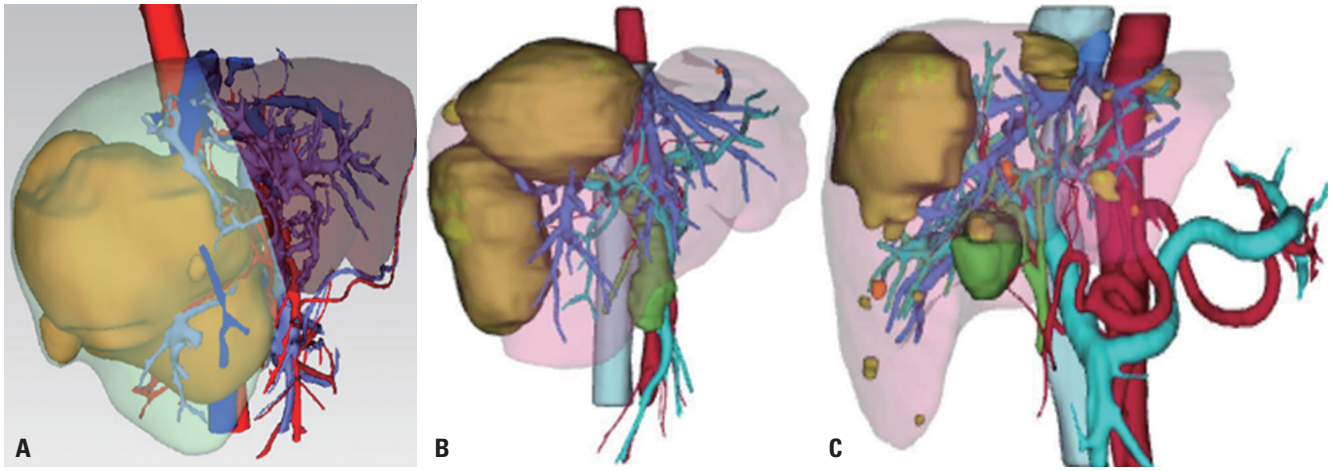

Fig. 1. 3D reconstruction of the liver tumors. (A) HCC (yellow color) in the right liver lobes. (B) Two CRLMs (yellow color) in the right liver lobes. (C) HCC and multiple intrahepatic metastases (yellow color). 3D, three-dimensional; HCC, hepatocellular carcinoma; CRLM, colorectal cancer liver metastasis.

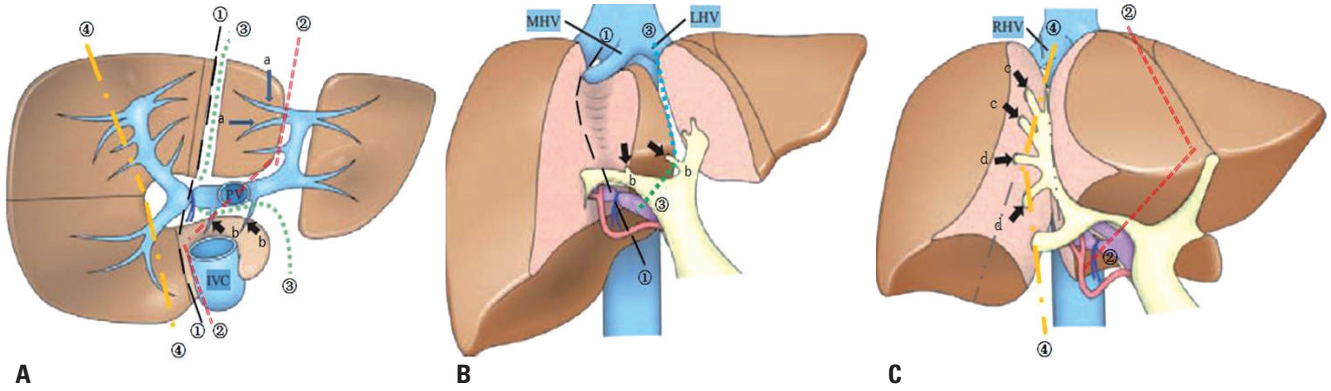

Fig. 2. The transection line for ablation in the 1st-stage operation. (A) Transverse section of the liver parenchyma in the 1st-stage operation. (B and C) Coronogram of the 1st-stage operation. ① indicates the transection line (black short lines) for hepatectomy of the right hemi-liver; ② indicates the transection line (red dotted line) for right hepatectomy plus S4 resection; ③ indicates the transection line (green dotted line) for right hepatectomy plus S1 resection; ④ indicates the transection line (yellow short lines) for right lateral sectoriectomy. Arrows (a) indicate the preserved portal pedicles in S4 for patients undergoing right hepatectomy plus S1 resection. Arrows (b) indicate the preserved portal pedicles in S1 for patients undergoing right hepatectomy plus S4 resection. Arrows (c) indicate the portal pedicals of S8 and arrows (d) indicate the portal pedicals of S5 that must be ligated for right hemi-hepatectomy. IVC, indicate inferior vena cava; PV, portal vein; LHV, left hepatic vein; MHV, middle hepatic vein; RHV, right hepatic vein.

hepatis. Then, a retro-hepatic tunnel was established, through which the liver was hung by an elastic strap. Partitioning of the liver parenchyma was performed using RFA (Habib 4X, RITA 4401L, Angio Dynamics Inc, Redwood City, CA, USA) guided by laparoscopic ultrasound (LUS, EUP-OL334, ALOKA, Osaka, Japan). For right hemi-hepatectomy, only the right portal vein was ligated, with the liver parenchyma ablated along the right side of the median fissure just to the right of the middle hepatic vein. For expected right hemi-hepatectomy plus S4 resection, the liver parenchyma was ablated along the right side of the umbilical portion of the left portal vein, preserving the S1 portal pedicles. For expected right hemi-hepatectomy plus S1 resection, the liver parenchyma was ablated just to the left side of the middle hepatic vein, continuing toward the ductus venosum and preserving the caudate portal pedicles. For extended right lateral sectoriectomy, where liver partitioning was slightly lateral to the main portal pedicle of the right paramedian sector, preserving the portal pedicles was achieved by ligating the portal vein of the right lateral sector. The partition area of the liver parenchyma during the 1st-stage operation is shown in Fig. 2. Parameters of Habib 4X were set at a working power of 70–80 watts, an ablation time of 5–6 min in each point, a point-to-point distance of 2.5–3 cm, and a depth arriving at the front wall of the hanging strap. After ablation, 0# absorbable sutures (polydioxanone suture) were left as labels for the right hepatic artery and right bile duct; the elastic strap of the retro-hepatic tunnel was also left. The 2nd-stage operation was performed via open surgery. After the right hepatic artery and right bile duct were transected separately, the elastic strap through the retro-hepatic tunnel was lifted, allowing for hepatectomy along the demarcated line formed by the 1st-stage operation, and the atrophied hepatic lobes were transected clearly up to the anterior wall of the inferior vena cava.

In the classic group, operations for both stages were per-

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formed via open surgery. In the 1st-stage operation, complete liver transection to the level of the inferior vena cava was carried out at the main portal fissure, the left portal fissure, the right portal fissure, or the anterior fissure of the right liver, depending on patient factors and local extent of the tumor, using a liver-hanging maneuver. In the 2nd-stage operation, the atrophic diseased liver lobes were resected in the same manner as that for the modified group.

Volume evaluation of FLR and FFLR

MDCT was performed in both groups 7 days after the 1st-stage operation for volume calculation of the FLR and was repeated at an interval of 6–8 days until FLR and FLR/BW values reached cutoff values deemed safe enough for the 2nd-stage operation (Fig. 3). Kinetic growth rate (KGR), defined as the degree of hypertrophy at initial volume assessment divided by days elapsed after the 1st-stage operation, was calculated.[9]

SPECT was used preoperatively and 1 week after the 1st-stage operation for evaluation of FFLR in both groups. Twenty minutes after intravenous injection of sodium phytate, dynamic scintigraphy and SPECT images were obtained every 25 seconds with a low-energy and high-resolution collimator. A total of 64 frames were collected around the human body. After image reconstruction, the functional liver volume was calculated by classical edge-tracing and representational pixel methods, and the average value calculated from both methods was recorded as the final result.[10]

Follow-up and statistical analysis

All patients were followed up routinely every 4–6 weeks after discharge until death or end of the study. The continuing medical history and results of laboratory tests for each patient were all recorded. Descriptive data are expressed as a mean±SD or median (interquartile range). Survival rate was calculated using the Kaplan-Meier method. Statistical comparisons of baseline data were performed using the Mann-Whitney U test, χ^2 test, or Fisher's exact test. Differences were considered significant with a two-sided p value below 0.05.

RESULTS

Clinical characteristics of the included patients

A total of 45 patients including 38 males and 7 females, who underwent modified ALPPS procedures formed the study group. Among them, 7 patients fulfilled inclusion criteria 1) for FLR (15.5%), 13 for criteria; 2) (28.9%), 16 for criteria; 3) (35.6%), and 9 for criteria; 4) (20.0%). For comparison, 34 patients, including 30 males and 4 females, who underwent classic ALPPS procedures were included. Among them, 19 patients were enrolled according to inclusion criteria 1) (55.9%), 8 according to criteria; 2) (23.5%), 5 according to criteria; 3) (14.7%), and 2 according to criteria; 4) (5.9%), with significant differences between groups (p<0.05). For patient-related variables, no obvious difference was found. Regarding tumor-related variables, the proportion of HCCs in the modified group was markedly higher than that in the classic group. Among liver-related variables, the proportions of liver cirrhosis or liver dysfunction in the modified group were higher. Accordingly, MELD scores were also higher in the modified group. No difference was found in preoperative therapy between groups (Table 1).

Surgical feasibility of ALPPS procedures

For 1st-stage operations, the median durations of surgery were 138.6 and 323.7 min, and the median intraoperative blood loss amounts were 165 and 520 mL in the modified (n=45) and classic groups (n=34; p<0.01), respectively. Blood transfusion rates were lower in the modified group than in the classic group (8.9% vs. 44.1%, p<0.01). The incidence of complications was also lower in the modified group (51.1% vs. 73.5%, p<0.05), although incidence of severe complications did not differ between the groups. For patients who underwent the 2nd-stage operation (n=43 in the study group and n=31 in the classic group), although the overall incidence of complications in the modified

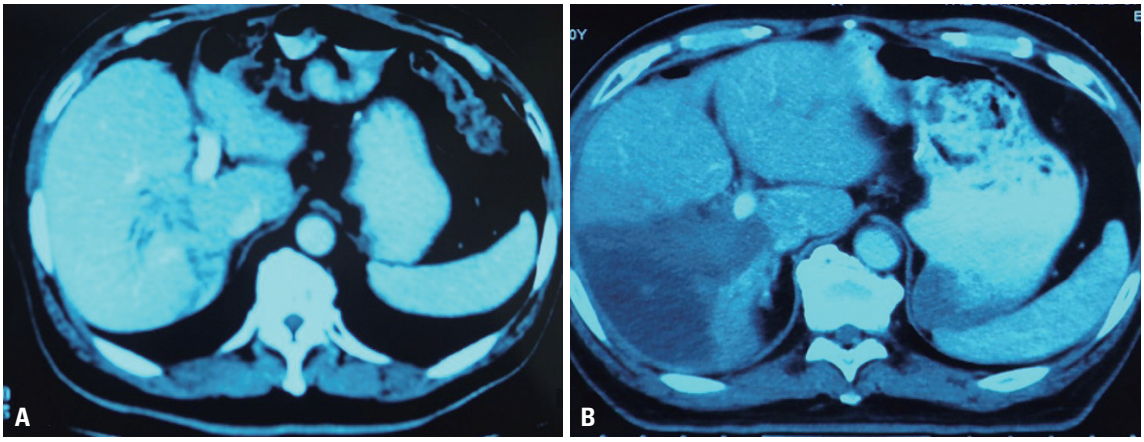

Fig. 3. Peri-operative CT images of a patient with HCC. (A) A large carcinoma (10×8.5×8.0 cm) in the right liver lobe before the 1st-stage operation. (B) Hyperplasia of the left liver lobe before the 2nd-stage operation. HCC, hepatocellular carcinoma.

Table 1. Patient and Tumor Characteristics

Variables	Modified ALPPS (n=45)	Classical ALPPS (n=34)	*p* value
Patient-related			
Sex			>0.999
Male	38 (84.4)	30 (88.2)	
Female	7 (15.6)	4 (11.8)	
Age, yr	47 (27–61)	51 (34–69)	0.175
Tumor-related			
Type of tumor			0.008*
HCC	31 (68.9)	8 (23.5)	
ICC	4 (8.9)	2 (5.9)	
CRMC	10 (22.2)	24 (70.6)	
Total tumor length, cm	13.7 (8.2–18.6)	11.6 (8.4–17.4)	0.310
Tumor number	2.1 (1–5)	2.8 (1–7)	0.483
Liver-related			
HBV-infection	34 (75.6)	6 (17.6)	0.032*
Liver cirrhosis	29 (64.4)	4 (11.8)	0.014*
Child-Pugh grading			<0.001
Grade A	39 (86.7)	34 (100)	
Grade B	6 (13.3)	0	
Grade C	0	0	
MELD score, points	16.4 (6–23)	9.6 (3–20)	0.035*
Treatment-related			0.220
Preoperative therapy	32 (71.1)	29 (85.3)	
TACE	13 (28.9)	3 (8.8)	
IV chemotherapy	7 (15.6)	9 (26.5)	
Targeted drug therapy	3 (6.7)	5 (14.7)	
Combined therapy	9 (20.0)	12 (35.3)	

ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; CRMC, colorectal metastatic cancer; HBV, Hepatitis B virus; MELD, Model of End-Stage Liver Disease; TACE, transcatheter arterial chemoembolization; IV, intravenous.
Data are presented as n (%).
*p<0.05.

group was slightly higher than that in the classic group (76.7% vs. 54.8%), the incidence of severe complications, as well as the duration of operation, weight of resected livers, classification of operation modus, intraoperative blood loss, blood transfusion rates, hospital days after operation, and mortality within 30 days, did not differ between groups. Details are provided in Table 2.

Analysis of complications and surgical death

No patient died after the 1st-stage operation in either group. While no intraoperative blood transfusions were performed in the modified group, 4 patients received blood transfusions during the interval period because of chronic anemia. Major complications after the 1st-stage operation in the study group included ascites (n=13, 28.9%), pleural effusion (n=12, 26.7%), and biliary fistula (n=6, 13.3%). Two patients were sent to the intensive care unit (ICU): one for acute respiratory distress syndrome (ARDS, Grade IVa), and the other for multiple organ dysfunction syndrome (MODS, Grade IVb). They both abandoned the 2nd-stage hepatectomy after recovery. In the classic group, intraoperative blood transfusions were performed in 8 patients (23.5%), more than that in the modified group (p=0.002). During the interval period, another 7 patients received blood transfusions because of chronic bleeding. Major complications in the classic group included biliary fistula (n=13, 38.2%), chronic bleeding (n=11, 32.4%), and pleural effusion (n=9, 26.5%). Two patients underwent selective angiographic embolization for liver bleeding (Grade IIIb), and 1 patient underwent emergent open surgery for bile leak with active liver bleeding (Grade, IVa). Two patients were sent to the ICU for ARDS (Grade IVa) and for MODS (Grade IVb). Among the 5 patients with severe complications, three (1 of Grade IVb and 2 of Grade IVa) abandoned the 2nd-stage operation.

During the 2nd-stage hepatectomy, intraoperative blood transfusions were performed for 7 patients in the modified group (16.3%) and for 3 patients in the classic group (9.7%), without statistical difference (p=0.635). Severe complications occurred in 7 patients in the modified group, including one with severe ascites (Grade IIIb, tension-reducing suture of the wound under general anesthesia was performed), three with active bleeding or liver stump abscess because of bile leak (1 of Grade IVa who underwent emergent open surgery for life saving, 1 of Grade IVb who underwent emergent surgery, and 1 death of Grade V), two with liver failure (ICU support, Grade IVb), and one with deadly MODS (Grade V). In the classic group, severe complications occurred in 3 patients, including one with liver failure (ICU support, Grade IVb) and two with deadly MODS (Grade V).

For the 2 patients who died within 30 days after the 2nd-stage hepatectomy in the modified group, they both had been diagnosed with HCC with Hepatits B virus (HBV)-infected liver cirrhosis. One died of sepsis with disseminated intravascular coagulation originating from bile fistula, resulting in grade C liver failure. The other one died of grade C liver failure. Postoperative death within 30 days occurred in 2 patients in the classic group: One with colorectal cancer liver metastasis (CRLM) and the other with HBV-infected HCC. Both died of MODS because of severe bile leakage. All four deaths had undergone red blood cell transfusion during the 2nd-stage operation.

Calculation of FLR and FFLR growth

In the study group, FLR before the 1st-stage operation was 388.6±122.5 cm^3; FLR/SLV (% FLR) was 33.8±8.6%; and FLR/BW was 0.78±0.14%. Interval days were 16.4±5.7 day. One week after the 1st-stage operation, FLR increased to 474.6±104.7 cm^3 (increase of 22.1±10.4%), and FFLR increased to 453.4±108.2 cm^3 (increase of 16.6±9.5%). During the interval period, FLR increased to 567.9±132.3 cm^3; FLR/SLV increased to 51.6±12.7%; and FLR/BW increased to 0.94±0.22%. The KGR in the modi-

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Table 2. Surgical Feasibility and Short-Term Outcomes of ALPPS Procedures

Variables	Modified ALPPS (n=45)	Classical ALPPS (n=34)	*p* value
1st-stage operation related			
Duration of the operation (range), min	138.6 (85–175)	323.7 (145–530)	<0.01*
Blood loss (range), mL	165 (80–470)	520 (280–1100)	<0.01*
Blood transfusion performance	4 (8.9)	15 (44.1)	<0.01*
Major complication	23 (51.1)	25 (73.5)	0.043*
Ascites	13 (28.9)	4 (11.8)	
Pleural effusion	12 (26.7)	9 (26.5)	
Bile leak	6 (13.3)	13 (38.2)	
Infection	4 (8.9)	6 (17.6)	
Bleeding	2 (4.4)	11 (32.4)	
ARDS	1 (2.2)	1 (2.9)	
MODS	1 (2.2)	1 (2.9)	
Clavien–Dindo classification			0.484
Grade I -IIIa	21 (91.3)	20 (80.0)	
Above Grade IIIb	2 (8.7)	5 (20.0)	
2nd-stage operation related			
Resection performed	43 (95.6)	31 (91.2)	0.745
Duration of the 2nd operation, min	305.3 (160–385)	237 (115–310)	0.264
Resected liver weight, g	512 (320–836)	553 (378–910)	0.375
Operation modus			0.952
2 segments resection	1 (2.4)	0	
3 segments resection	7 (16.3)	5 (16.1)	
Right hemihepatectomy	14 (32.6)	9 (29.0)	
Extended right hemihepatectomy	6 (14.0)	6 (19.4)	
Right hemihepatectomy+s1 resection	8 (18.6)	6 (19.4)	
Right hemihepatectomy+s4 resection	7 (16.3)	5 (16.1)	
Blood loss (range), mL	575 (350–950)	392 (250–820)	0.473
Blood transfusion performance	21 (48.8)	12 (38.7)	0.387
Major complication	33 (76.7)	17 (54.8)	0.047*
Bile leak	8 (18.6)	6 (19.4)	
Bleeding	5 (11.6)	2 (6.5)	
Infection	9 (20.9)	5 (16.1)	
Ascites	15 (34.9)	8 (25.8)	
PHLF	5 (11.6)	3 (9.7)	
MODS	1 (2.3)	2 (6.5)	
Clavien-Dindo classification			0.941
Grade I–IIIa	26 (78.8)	14 (82.4)	
Above Grade IIIb	7 (21.2)	3 (17.6)	
Hospital day after the 2nd operation	15.8 (6–29)	12.6 (7–23)	0.427
Mortality (≤30 day)	2 (4.7)	2 (9.7)	0.855

ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; ARDS, acute respiratory distress syndrome; MODS, multiple organ dysfunction syndrome; PHLF, post-hepatectomy liver failure.
Data are presented as n (%).
*$p<0.05$.

fied group was 10.9±5.2 cm^3/day. Compared with the modified ALPPS group, patients in the classic group had similar preoperative FLR (367.8±103.7 cm^3, p=0.445), FLR/SLV (31.7±9.4%, p=0.322), and FLR/BW (0.74±0.18%, p=0.286). Just before the 2nd-stage operation, variables in the modified group, including FLR (574.3±126.4 cm^3, p=0.835), FLR/SLV (54.7±11.6%, p=0.287), and FLR/BW (0.97±0.26%, p=0.594), were similar to those in the classic group. No obvious differences were found in total increases in FLR volume and % FLR during the interval period between the two groups (179.3±72.4 cm^3 vs. 206.5±64.3 cm^3, p=0.099; 46.1±22.9% vs. 56.1±25.7%, p=0.146). Perhaps because of the higher proportion of cases of liver cirrhosis re-

lated to HBV-infection, which prolonged the recovery days of impaired liver function, the interval days of the modified ALPPS group were longer than those in the classical ALPPS group (10.9±5.2 cm^3/day, $p<0.05$), and the KGR of the modified ALPPS group was less than that of the classic ALPPS group (16.3±8.6 cm^3/day, $p<0.05$). However, for 1 week after the 1st-stage operation, both FLR and FFLR increases in the classic ALPPS group (26.7± 12.1% and 20.1±10.3%) were similar to those in modified ALPPS group. All data are listed in Table 3.

Table 3. Morphological and FFLR Assessment

Variable	Modified ALPPS (n=43)	Classic ALPPS (n=31)	*p* value
Preoperative FLR (cm^3)	388.6±122.5	367.8±103.7	0.445
Preoperative FLR/SLV (%)	33.8±8.6	31.7±9.4	0.322
Preoperative FLR/BW (%)	0.78±0.14	0.74±0.18	0.286
Interval time (day)	16.4±5.7	12.7±4.3	0.023*
FLR at 1 week after stage 1 (cm^3)	474.6±104.7	466.2±116.3	0.746
FLR increase ratio (%)	22.1±10.4	26.7±12.1	0.199
FFLR at 1 week after stage 1 (cm^3)	453.4±108.2	441.6±113.5	0.652
FFLR increasing ratio (%)	16.6± 9.5	20.1±10.3	0.440
FLR before stage 2 (cm^3)	567.9±132.3	574.3±126.4	0.835
FLR/SLV before stage 2 (%)	51.6±12.7	54.7±11.6	0.287
FLR/ BW before stage 2 (%)	0.94±0.22	0.97±0.26	0.594
Total FLR increase (cm^3)	179.3±72.4	206.5±64.3	0.099
Total FLR increase ratio (%)	46.1±22.9	56.1±25.7	0.146
KGR (cm^3/day)	10.9±5.2	16.3±8.6	0.012*

FLR, future liver remnant; FFLR, functional FLR; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; SLV, standardized liver volume; BW, body weight; KGR, Kinetic growth rate.
*$p<0.05$.

Follow-up information and survival analysis

All patients who finished ALPPS procedures have been followed up. In the modified ALPPS group (n=41), the follow-up time was 19.7±2.1 month, and 14 patients (34.1%) were still alive at the time of data analysis. The median survival time was 21.8 (3.2–31.4) months. Kaplan-Meier survival curves are shown in Fig. 4. Four patients with HCC died within 6 months because of lung and/or brain metastasis; one with liver metastasis from sigmoid carcinoma died of cerebrovascular accident within 12 months, and the other 22 all died of tumor recurrence. For comparison, the follow-up time in the classic ALPPS group (n=29) was 21.2±2.8 months, and the median survival time was 22.3 (2.5–61.8) months, indicating no difference between the two groups ($p>0.5$). Except for 3 patients (10.3%) who were still alive, 1 patient with intrahepatic cholangiocarcinoma (ICC) and three with HCC died of liver failure within 3 months, one with HCC died of lung metastasis within 6 months, and the other 21 all died of tumor recurrence.

DISCUSSION

Achieving a safe tumor resection has remained a research hotspot in the field of liver surgery. It takes at least 4–6 weeks for TACE, portal vein embolism (PVE), and portal vein ligation (PVL) to increase the FLR volume by 20%–40%, and no more

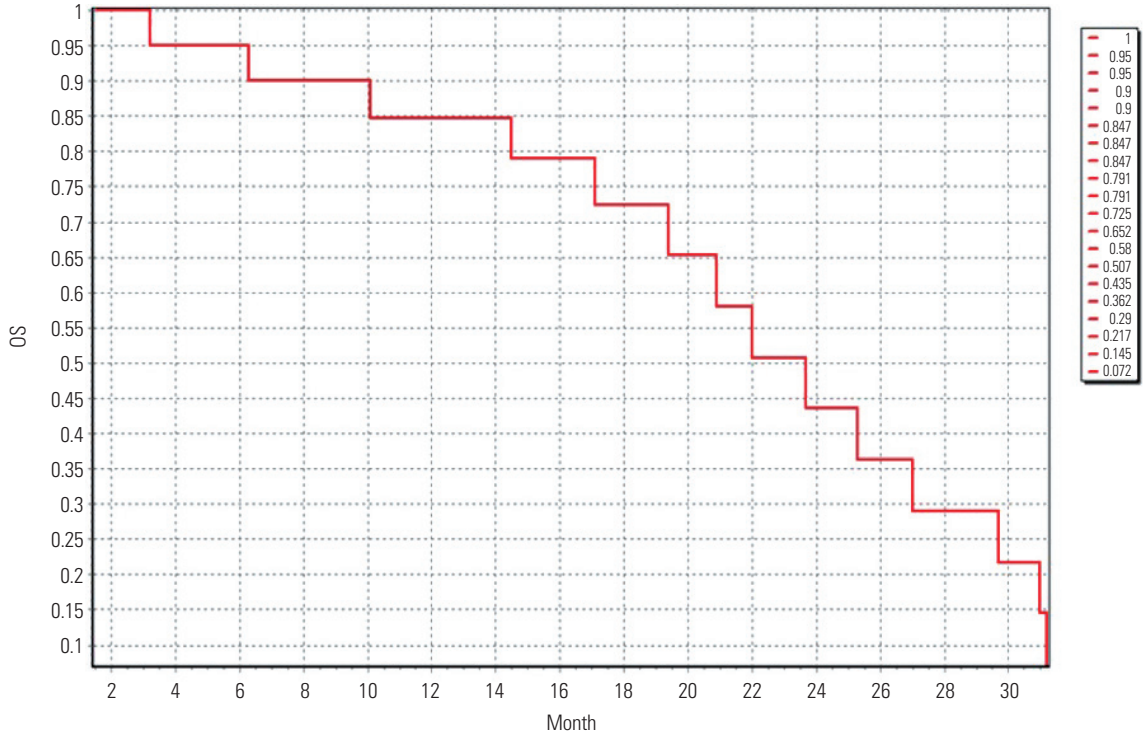

Fig. 4. OS for the modified ALPPS group. OS, overall survival; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy.

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than 10% of patients really benefit from these methods. The long wait for FLR to increase can lead to cancer metastasis, and most patients may lose the chance for radical resection.[11,12] Since its first performance in 2007 by Dr. Schlitt in Germany, ALPPS has been found to be effective in increasing FLR rapidly. The reported interval of ALPPS can reach up to 10.3 days, much shorter than PVL or PVE, and tumor progression during such interval could be negligible.[7,8,10] During the initial practice of ALPPS, the 1st-stage operation was often performed by complete parenchymal transection and ligation of the right portal vein (classic ALPPS) through open surgery. The classic 1st-stage operation results in two large wound surfaces on the liver, doubling the incidence of bile leak and infection, that lead to severe and extensive adhesion, making the 2nd-stage operation difficult to perform. Moreover, massive bleeding or repeated porta hepatis occlusion typically accompanies the classic 1st-stage operation, prolonging postoperative recovery.[13,14] Therefore, many surgeons believe that a balance between rapid FLR increase and trauma reduction in the 1st-stage operation is crucial for successful ALPPS.[15] In initial ALPPS practice, we strictly selected individuals only with normal liver condition, avoiding HBV-infected or liver cirrhosis, and although the short-term outcomes were satisfactory, the scope of ALPPS had remained restrained.

Research has demonstrated that tumor type is an independent risk factor for poor outcomes with ALPSS, with morbidity and mortality rates for CRLM lower than those for primary hepatobiliary malignancies.[16] Nevertheless, we noticed that complication rates after ALPPS for CRLM are still higher than those after conventional liver resection. Although there was no matched pair analysis, patients undergoing ALPPS had more advanced disease and a higher tumor burden than those treated by extended hepatectomy after PVE or PVL, and potential selection bias in the ALPPS group may partly account for the poor prognosis. We speculate that the functional condition of FLR should be the foundation of patient selection for ALPPS, not just tumor type. Indeed, much better results have been obtained by applying strict criteria for HCC candidates for ALPPS through ALICE, which decreased the 90-day mortality rate to 7.1% and effectively extended the application scope of ALPPS.[17] Although the degree of FLR hypertrophy in fibrotic/cirrhotic livers appears somewhat less in non-cirrhotic livers, appropriate parenchymal transection seems to be associated with much more rapid hypertrophy of FLR than PVE, and experiences from studies in Hong Kong, Rome, and Fudan suggest that in selected patients, ALPPS seems to be an attractive approach to increase resectability in HCC patients otherwise left with palliative treatment options.[15,17,18] Based on this, we addressed the usage of ALICE in patient-selection for meticulous risk evaluation before ALPPS.

We used a 3D reconstruction system based on CT images to analyze intrahepatic anatomy and to obtain information on the blood supply to the tumor, the reflux system of the liver segments occupied by the tumor, and FLR volume to determine the range of hepatectomy. By means of 3D reconstruction, we could calculate the blood supply of the portal venous system, assess FLR accurately, and design each operation guided by the Couniaud segmenting principle.[18] During the course of preoperative planning, special attention was paid to the vascularization and biliary drainage of the preserved liver segments in order to avoid ischemia/necrosis or bile leakage. At the end of the 1st-stage operation, bile duct ligation of the future specimen was considered absolutely contraindicated as it might cause cholestasis, cholangitis, or bile leaks.[15,17,18] Therefore, postoperative complications from bile leakage were significantly reduced, thus preventing or minimizing adhesions and reduce bleeding and trauma during the 2nd-stage operation. Clinical trials have reported the same effect of rapid liver hyperplasia by partial liver parenchyma disconnection (50%–80%) as by complete disconnection,[18,19] based on which in-situ and non-transection liver partition by means of LUS and RFA in the 1st-stage operation were performed in the modified group. Although the proportions of liver cirrhosis and Grade B liver damage in the modified group were much higher, no difference was found in FLR and FFLR increase between the modified and classic groups at 1 week after the 1st-stage operation. Although the overall increase in FLR was lower and the interval days were longer in the modified group, reflecting the severely impaired liver reserve function and delayed liver recovery, it was only connected with the principle of patient selection. Although most patients (64.4%) in the modified group presented with HBV-related liver cirrhosis, with 13.3% of them having Grade B liver damage, the success rate could reach 95.6%, and the mortality was controlled under 5%, much better than that in most reports in the literature.

CT-scan volumetry, even when based on 3D reconstruction, has not been found to be correlated with liver function.[20] Hepatobiliary scintigraphy using 99mTc-labeled iminodiacetic acid derivates could show that volumetry overestimates liver function in ALPPS.[20,21] The mechanisms of the discrepancy between volume increase and the high rate of liver failure in ALPPS are not fully understood and may be attributed to initial edema and enlarged, but still at least partially immature and not completely functioning hepatocytes, within the initial period of regeneration.[22] This warranted an assessment of both function and volume of the FLR during the interstage course of ALPPS. During the initial attempt of ALPPS procedures, we realized the importance of accurate assessment of both FLR and FFLR. Although we only used MDCT to perform initial preoperative planning, which posed bias in patient-selection, to avoid patients with liver cirrhosis, we used SPECT to calculate FFLR in of our study groups to ensure the safety of all patients after ALPPS procedures. SPECT offers quantitative information regarding segmental liver function and therefore provides an accurate measure of FFLR. Meanwhile, preliminary reports have shown that KGR is a predictor for postoperative liver failure after ALPPS with a cutoff-point of 6% per day.[9,22]

The OS in the modified ALPPS group was 19.7 months, similar with that in the classic group and reports in the literature. However, in consideration of the clinical staging of the tumors and the proportions of liver cirrhosis, we can conclude that the modified strategy provides satisfactory survival. It was reported that the duration of the 1st-stage operation and intraoperative red blood cell transfusion were independent risk factors for postoperative survival.[22] In contrast to classic ALPPS, the surgical extent and the associated trauma of the 1st-stage operation were dramatically reduced while the main surgical steps were performed at the 2nd-stage operation. Although the short-term clinical outcomes were similar in both groups, overall trauma in the modified ALPPS group was significantly reduced, especially when considering that most of the patients in the modified group presented with primary liver malignancies with liver cirrhosis of different degrees. Our risk-reduced strategy could embody the benefits of ALPPS and significantly expand the scope of its application.

Notwithstanding, ALPPS is still not a mature surgery. Much work is needed to reduce the incidence of complications. We are collecting more adaptable patients in corporation with more institutions prospectively for future study and conducting more detailed grouping analysis according to the extent of hepatectomy in ALPPS procedures by randomized controlled trials containing more cases.

In conclusion, according to our study, ALPPS with risk-reduced modifications could be a feasible treatment for patients with large hepatocarcinoma. We expect it to provide long-term survival for patients with moderate liver cirrhosis without enough FLR volume.

AUTHOR CONTRIBUTIONS

Conceptualization: Ya-Lin Kong and Hong-Yi Zhang. Data curation: Ying Xing. Formal analysis: Ying Xing and Jie Li. Funding acquisition: Hong-Yi Zhang. Investigation: Cheng-Li Liu. Methodology: Ling-Hong Kong. Project administration: Cheng-Li Liu and Xu Han. Resources: Cheng Wang. Software: Jie Li. Supervision: Jiang-Min Chen. Validation: Xiao-Jun He. Visualization: Xu Han. Writing—original draft: Ya-Lin Kong. Writing—review & editing: Hong-Yi Zhang. Approval of final manuscript: all authors.

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