Original Article

Trans-arterial chemo-emobilization (TACE) combined with laparoscopic portal vein ligation and terminal branches portal vein embolization for hepatocellular carcinoma: a novel conversion strategy

Qing Yan[1#], Feng-Jie Wang[1#], Jia-Wei He[2], Jian-Yuan Hu[1], Eric C. H. Lai[3], Huan-Wei Chen[1^]

[1]Department of Hepatic Surgery, First People's Hospital of Foshan, Foshan, China; [2]Department of Radiology, First People's Hospital of Foshan, Foshan, China; [3]Department of Surgery, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China

Contributions: (I) Conception and design: HW Chen; (II) Administrative support: ECH Lai, HW Chen; (III) Provision of study materials or patients: FJ Wang, JW He, JY Hu; (IV) Collection and assembly of data: Q Yan, FJ Wang; (V) Data analysis and interpretation: Q Yan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Huan-Wei Chen, BM. Department of Hepatic Surgery, First People's Hospital of Foshan, No. 81, North Lingnan Avenue, Chancheng District, Foshan 528000, China. Email: chwei_fsyyy@163.com.

Background: Hepatocellular carcinoma (HCC) is currently one of the most common malignant tumors with the highest mortality rates in the world. Most patients with HCC have lost the opportunity for surgery at the time of initial diagnosis. This study aims to introduce a new conversion strategy: trans-arterial chemo-emobilization (TACE) combined with laparoscopic portal vein ligation (PVL) and terminal branches portal vein embolization (PVE).

Methods: From November 2018 to February 2023, patients with HCC and insufficient future liver remnant (FLR) were included for this novel treatment strategy. At first, TACE was performed. Then, these patients underwent laparoscopic PVL and terminal branches PVE. After hypertrophy of FLR, these patients underwent the second stage of liver resection. All patients were followed up regularly postoperatively.

Results: A total of 13 patients with HCC were included. All patients underwent the TACE and the first stage of laparoscopic PVL and terminal branches PVE. After a mean of 28.7 days after the first stage of operation, the FLR increased by a mean of 183.4 cm^3, equivalent to 49%. All patients underwent the second stage of liver resection. There was no surgical mortality. The mean postoperative hospital stay was 9.1 days. The median survival was 24.5 months.

Conclusions: The treatment strategy of preoperative TACE combined with laparoscopic PVL and terminal branches PVE and second stage of liver resection is a preliminarily feasible and relatively safe new strategy which deserves further exploration in the future.

Keywords: Hepatocellular carcinoma (HCC); portal vein ligation (PVL); portal vein embolization (PVE); liver resection; regional therapy

Submitted Jul 03, 2024. Accepted for publication Sep 23, 2024. Published online Oct 29, 2024.
doi: 10.21037/jgo-24-507
View this article at: https://dx.doi.org/10.21037/jgo-24-507

^ ORCID: 0000-0001-8843-6754.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor in the world in terms of incidence and second in mortality (1). The prognosis of patients with HCC is relatively poor, and surgical resection is the most common curative method (2,3). However, due to the insidious onset and rapid progress of it, many patients have lost the opportunity for surgery at the first diagnosis (4). Insufficient future liver remnant (FLR) is one of the most important factors determining the resection rate of HCC. In order to avoid postoperative liver failure and mortality due to insufficient FLR, it is extremely important to accurately assess the patient's liver function status and size of FLR before surgery. It has been reported in the literature that for patients with indocyanine green retention test after 15 min (ICG R15) <10% and without cirrhosis, at least 30% of FLR is required, while patients with cirrhosis require at least 50% of FLR (5). In order to allow more HCC patients to receive curative surgery without postoperative liver failure, surgeons have explored many methods to increase the FLR volume before surgery such as portal vein embolization (PVE), portal vein ligation (PVL) and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) (6). PVE refers to embolizing the portal vein on the resected side with various embolic materials. PVL refers to surgical ligation of the patient's portal vein on the resected side, and ALPPS is a two-step hepatectomy combined with liver separation and PVL, which not only further cuts off the liver parenchyma on the basis of ligating the portal vein on the resected side, and reduces the blood flow from the remnant side to the resected side. These three surgical methods are widely used in clinical practice, but these methods still have some drawbacks. The waiting time for liver remnant hypertrophy after PVE and PVL is too long, and the increase in liver volume is not very obvious (7). ALPPS has the most obvious increase in liver volume, but the operation is more complicated, and the postoperative complications and perioperative mortality are higher (8). With the development of local-regional therapy and immunotherapy in recent years, through the combination of tumor size reduction and increased size of FLR increases the chance of curative resection of patients with HCC. This study reported the safety and effectiveness of a novel treatment strategy of preoperative trans-arterial chemo-emobilization (TACE) combined with first stage of laparoscopic PVL and terminal branches PVE and second stage of liver resection in increasing the resectability of patients with HCC. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-507/rc).

Highlight box

Key findings

- This new conversion strategy could increase the future liver remnant (FLR) efficiently and safely.

What is known and what is new?

- Portal vein embolization (PVE) and portal vein ligation (PVL) could improve the FLR safely but the time interval is too long; associating liver partition and portal vein ligation for staged hepatectomy have the high efficiency of FLR increasement but the perioperative mortality and complication rate were also higher.
- This new conversion strategy combined trans-arterial chemo-emobilization with laparoscopic PVL and terminal branches PVE, which could improve the efficiency of FLR increasement and decrease the perioperative complication rate.

What is the implication, and what should change now?

- This conversion strategy is suitable for hepatocellular carcinoma (HCC) patients without enough FLR, it could be performed under laparoscopy, which reduces the trauma of the first operation and is conducive to the recovery of patients after surgery. For suitable cases, the second operation could also be completed under laparoscopy.
- Multi-center, large-scale clinical trial verification is needed in the future to verify the safety and efficiency of this new conversion strategy for HCC patients.

Methods

From November 2018 to February 2023, 13 patients with HCC and insufficient FLR hospitalized in the Department of Hepatic Surgery were included for the novel treatment strategy. At first, TACE was given to control the tumor. Then, these patients underwent laparoscopic PVL and terminal branches PVE. After hypertrophy of FLR, these patients underwent the second stage of liver resection. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all the patients, and this study was approved by the ethics committee of The First People's Hospital of Foshan (No. FSYYY-EC-SOP-008-02.01-A09). Patients were followed up regularly in the outpatient clinic until July 23, 2023. α-fetoprotein (AFP), biochemical and imaging examinations were regularly performed.

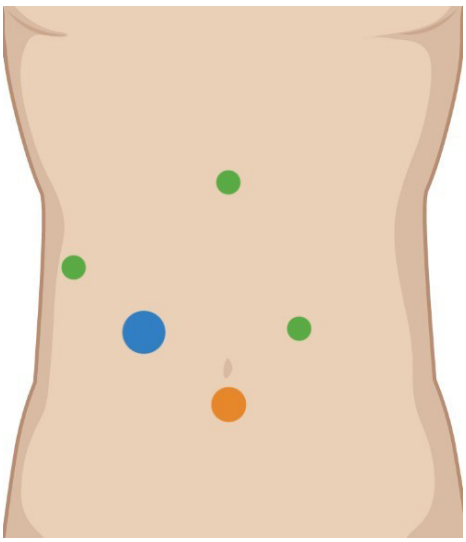

Figure 1 Schematic diagram of laparoscopic trocar position: Blue circle refers to main operation hole (12 mm). Orange circle refers to observation hole (10 mm). Green circle refers to assistant operation hole (5 mm).

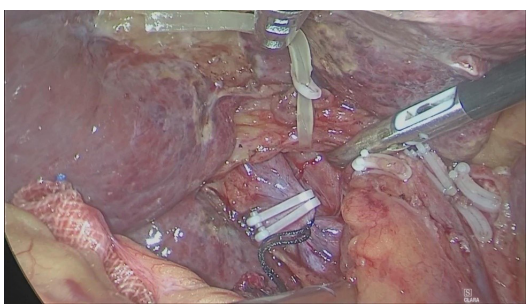

Figure 2 Dissect the first hepatic portal and right branch of the portal vein, and ligate it proximally.

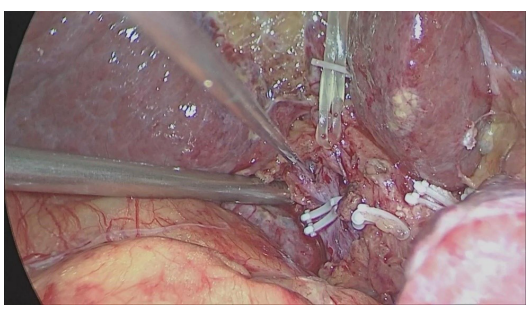

Figure 3 An 18G needle was punctured to the distal end of the right portal vein percutaneous, withdraw the needle core, and insert the guide wire.

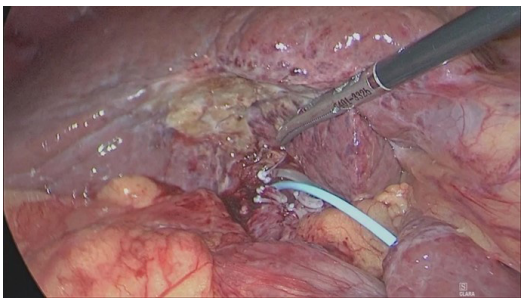

Figure 4 The guide wire was inserted into the right posterior branch of the portal vein under X-ray fluoroscopy, and the 5F catheter was inserted along the guide wire.

Surgical technique

Preoperative TACE

The TACE was performed in the interventional department of our hospital. The patient was placed in a supine position, and the right femoral artery was cannulated using the Seldinger technique, after that, it was ascending by angiography and over selected to the feeding artery of liver tumor. Nedaplatin, lipiodol and embolic particles were slowly injected under fluoroscopy, and the embolic effect was detected by postoperative angiography. The specific intraoperative drugs and dosage will be slightly adjusted by the interventional specialists of our hospital according to the personal situation of the patients.

First stage and second stage of operations

The first operation was completed in our hybrid operation room. The patient was placed in a left oblique supine position with head high and feet low, and entered into the abdomen with a five-port method (*Figure 1*). After cholecystectomy, the right branch of the portal vein was dissected and then ligated with 7/0 Silk, then controlled with double clips (*Figure 2*), then an 18G needle was punctured to the distal end of the right branch of the portal vein percutaneously, and the needle core was removed and the guidewire was inserted (*Figure 3*). The guidewire was placed into the right posterior branch of the portal vein under intraoperative X-ray fluoroscopy, and the 5F catheter was placed along the guide wire (*Figure 4*). Firstly, a 350 μm polyvinyl alcohol particle embolic agent (PVA) was slowly injected into the terminal branch of the right posterior portal vein, and then a 560 μm PVA was given to embolize the main trunk of right posterior portal vein (*Figure 5*). Secondly, the same method was used to embolize

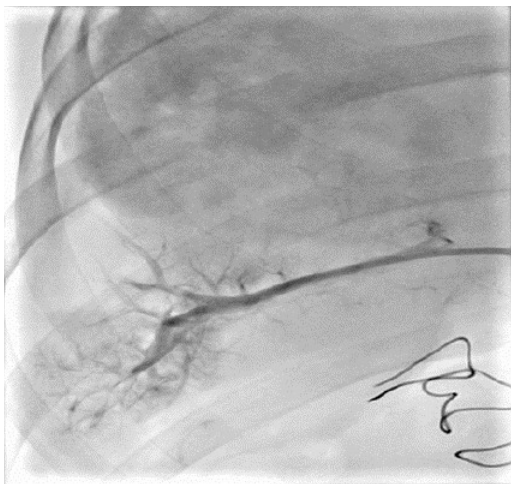

Figure 5 After intraoperative portal vein angiography showed that the catheter had been inserted into the end of the right posterior branch of the portal vein, a piece of 350 and 560 μm particle embolic agent was slowly injected to embolize the end of the right posterior branch and the main branch of the portal vein.

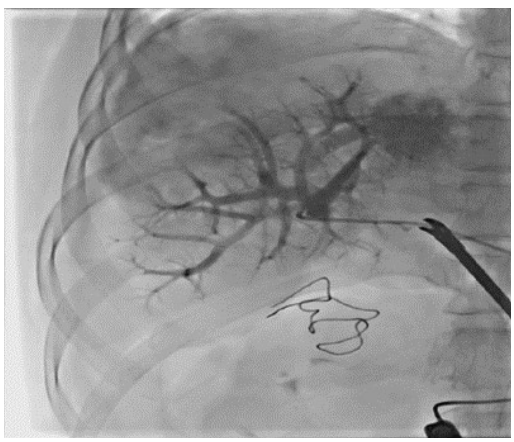

Figure 6 After intraoperative portal vein angiography showed that the catheter had been inserted into the end of the right anterior branch of the portal vein, a piece of 350 and 560 μm particle embolic agent was slowly injected to embolize the end and main branch of the right anterior branch of the portal vein.

the right anterior portal vein and its terminal branch (*Figure 6*). After angiography confirmation of the complete occlusion of the right anterior and posterior branch portal vein and its terminal branch, the catheter was removed, and the right portal vein was clamped with absorbable clamps at the puncture site. After the first stage operation, the timing of the second stage operation was determined according to the degree of FLR hypertrophy and the condition of the patient. The patient underwent right hepatectomy or extended right trisectionectomy according to the original surgical plan.

Volumetric analysis

Three-dimensional (3D) computed tomography (CT) reconstruction was performed to calculate the volume of each liver segment. The standard liver volume of patients was calculated according to the height and body weight (9). FLR is the expected sum of the remaining segment volumes after surgery. The FLR increasement rate was calculated using this formula: FLR increasement rate = (post-FLR – pre-FLR) / pre-FLR (%).

Statistical analysis

The statistical analysis was performed using SPSS software (V. 25.0). Numeric data were expressed as mean ± standard deviation (SD). The estimated survival was analysed by Kaplan-Meier curve plotting, and the survive curve was draw using GraphPad Prism 8.0.2.

Results

A total of 13 patients underwent this novel therapy successfully. Among them, 9 were males and 4 were female, with an average age of 51.38±8.13 years. The characteristic of the patients is shown in *Table 1*. Twelve of these patients had hepatitis B and had received entecavir antiviral therapy before surgery. All had Child-Pugh grade A liver function. The average AFP at admission was 6,369.75±12,094 ng/mL.

After the preoperative TACE, the tumors of 8 patients were reduced to a certain extent, and the tumors of 5 patients had static tumor size. The mean interval between TACE and first stage of operation was 37 days (range, 30–44 days). In the first stage of operation, the mean operation time was 3.5±0.5 h, the intraoperative blood loss was 25 mL (range, 15–35 mL). The liver enzyme increased temporarily after the operation, but all decreased to the normal level within 1 week after the operation. All patients had no complications. After a mean of 28.7 days after the first stage of operation, the FLR increased by a mean of 183.4±65.26 cm^3. The FLR increased a mean of 49%±15.87% (*Figure 7*). The mean interval between first stage of operation and second stage of operation was 28.69 days (range, 24–35 days). All patients underwent the second stage of liver resection. Four patients successfully

Table 1 Basic characteristics of patients

Patient	Sex	Age (years)	HBsAg	Child-Pugh grade	AFP level (ng/mL)	ICG	Cirrhosis	Tumor number	Tumor size (cm)	Vascular invasion
1	1	49	1	A	202.98	1.6	1	1	3.4	0
2	1	49	1	A	254	5.5	0	2	6.3; 7.8	0
3	1	53	1	A	93.55	17.3	1	1	10.5	1
4	0	51	1	A	34.91	3.9	1	1	16	1
5	1	59	1	A	11,547.23	5.9	1	1	5.5	0
6	0	61	1	A	41,657.3	2.2	1	1	6.2	0
7	1	57	1	A	3.59	9.8	1	1	8.5	0
8	0	50	1	A	5178	2.1	1	1	5	0
9	0	45	1	A	4.79	6.1	1	2	11; 3	0
10	1	32	1	A	3,288	11.5	1	1	12	0
11	1	64	0	A	106.8	4.9	1	1	2.6	1
12	1	47	1	A	1,063.55	9.2	1	1	8	0
13	1	51	1	A	19,372	16.3	1	1	6	1

HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; ICG, indocyanine green.

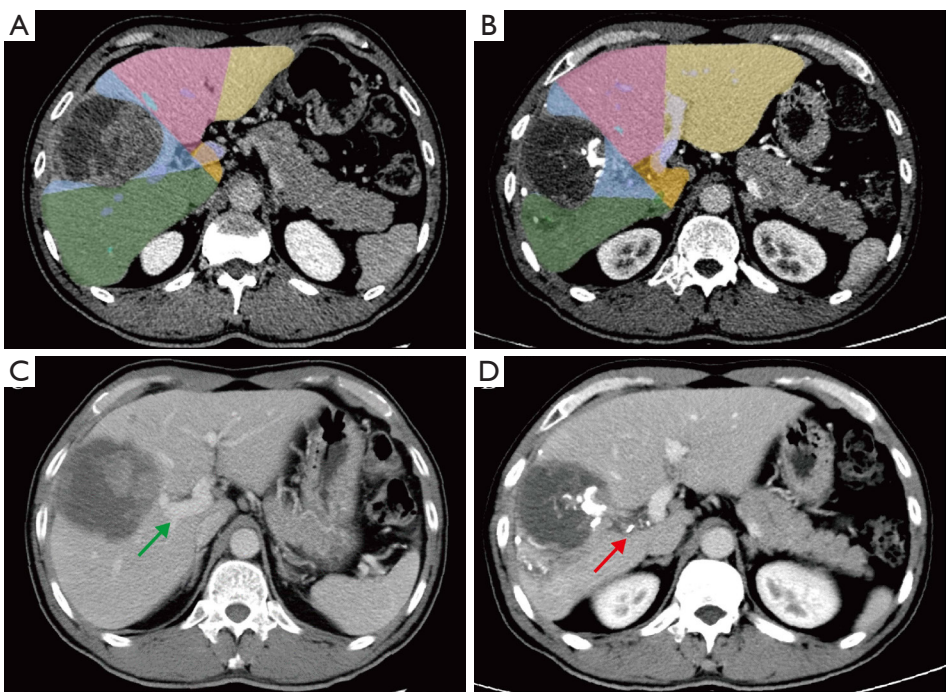

Figure 7 The CT examination showed that the FLR was obviously increased after the first step surgery, while the liver volume of diseased side was decreased. The yellow area shows left lateral lobe, the red area shows the left medial lobe, the blue area shows right anterior lobe, the green area shows right posterior lobe. (A) The 3D reconstruction of CT scan before the surgery. (B) The 3D reconstruction of CT scan after the surgery. (C) The CT scan of the liver revealed filling of the right portal vein (green arrow). (D) The CT scan of the liver revealed complete occlusion of the right portal vein (red arrow). CT, computed tomography; FLR, future liver remnant.

Table 2 The result of two-step surgery treatment

Patient	Preoperative treatment	Tumor stage	Pre-FLR	Time interval (day)	Post-FLR	FLR increasement	Second surgery
1	TACE	T1bN0M0 IB	271.7 (30.6%)	24	395.1 (44.5%)	45.40%	Laparoscopic right hemihepatectomy
2	TACE	T3N0M0 IIIA	293.5 (23.4%)	33	497.2 (39.6%)	69.40%	Right trilobectomy
3	TACE	T4N0M0 IIIB	446.9 (37.8%)	35	557.5 (47.1%)	24.70%	Laparoscopic right hemihepatectomy
4	TACE	T4N0M0 IIIB	331.9 (36.7%)	28	432 (47.8%)	30.16%	Right hemihepatectomy
5	TACE	T1bN0M0 IB	365.6 (31.2%)	29	590.7 (50.4%)	64.57%	Right hemihepatectomy
6	TACE	T1bN0M0 IB	354.3 (32.9%)	27	526.3 (48.9%)	48.50%	Laparoscopic right hemihepatectomy
7	TACE	T1bN0M0 IB	303 (25.3%)	30	495.9 (41.4%)	63.70%	Right hemihepatectomy
8	TACE	T1bN0M0 IB	355.2 (31.8%)	28	479 (42.9%)	34.90%	Right hemihepatectomy
9	TACE	T3N0M0 IIIA	422 (34.1%)	27	692 (55.9%)	64%	Right hemihepatectomy
10	TACE	T1bN0M0 IB	485 (36.7%)	29	724 (54.9%)	49.30%	Right hemihepatectomy
11	TACE	T4N0M0 IIIB	403 (36.3%)	28	626 (56.4%)	55.30%	Right hemihepatectomy
12	TACE	T1bN0M0 IB	431.7 (35.7%)	28	541.1 (44.8%)	25.30%	Laparoscopic right hemihepatectomy
13	TACE	T4N0M0 IIIB	472 (37.0%)	27	763.6 (59.9%)	61.80%	Right hemihepatectomy

FLR, future liver remnant; TACE, trans-arterial chemo-embolization.

underwent laparoscopic right hepatectomy, 8 patients underwent right hepatectomy and 1 patient underwent right trisectionectomy (*Table 2*). The mean operating time of second stage operation was 7.5±0.92 hours. The mean intraoperative blood loss was 778.46 mL (range, 400–1,000 mL). After surgery, one patient developed biliary fistula, and four patients had complications of pleural effusion. The overall complication rate was 38.5% (n=5), and there was no surgical mortality. The mean postoperative hospital stay was 9.08±1.71 days.

In addition, 5 of the 13 patients included in this study received oral targeted drugs (lenvatinib) before surgery, and one patient received a combination of camrelizumab and Apatinib. After the surgery, 10 patients were treated with lenvatinib and one patient was treated with camrelizumab and apatinib.

After a median follow-up of 13 months (range, 5–45 months), 2 of the 13 patients had intrahepatic recurrence, and two patients had extrahepatic metastases. Two patients died due to intrahepatic recurrence. The median survival was 24.5 months. The postoperative survival and recurrence of 13 patients are shown in *Figure 8*.

Discussion

The prognosis of patients with HCC is extremely poor, and surgical resection is the only curative method. The most serious complication of extensive liver resection is postoperative liver failure, and insufficient FLR is the main cause of postoperative liver failure (10). In order to ensure that the remaining liver volume after surgery could meet the normal needs of the body, surgeons use a variety of methods to shrink the liver tumor size and increase the FLR of the liver to be preserved. This increases the resectability of patients with HCC.

There are three main methods currently used, one is PVE, the second is PVL, and the third is ALPPS. These three methods could effectively increase the FLR, so as to obtain the opportunity of second stage surgical resection, but they also have their own drawbacks. Also, It should be considered that the increase of residual liver volume is not necessarily equivalent to the increase of liver function (11). In addition to the volume, it is still necessary to comprehensively evaluate the improvement of liver function through other indicators such as liver metabolic function

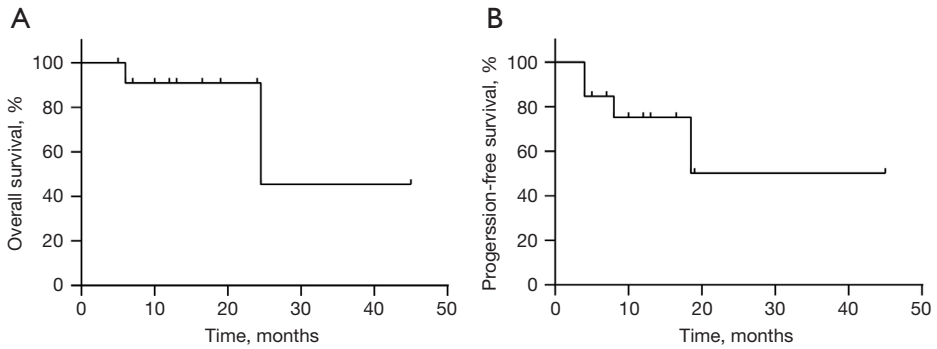

Figure 8 The survival status of patients after surgery. (A) The overall survival curve of patients. (B) The progression-free survival of patients.

and synthetic function related indicators.

PVE is a relatively safe and minimally traumatic method. Serious postoperative complications are rare, but there are also some disadvantages (12): (I) there are complications such as steel ring displacement, ectopic embolism, and intra-abdominal hemorrhage, which may lead to surgical failure. (II) The time interval between surgery is long, about 4 weeks on average. During the waiting period, tumor metastasis may occur, and the opportunity for surgical resection may be lost. The completion rate of the second-stage operation is relatively low. (III) PVE could only block the blood flow from the right main portal vein, but there are communicating branches between the resection side and the residual side portal vein, and the portal vein branches still have blood flow, which affects the effect of liver regeneration. It was reported in the literature that the liver volume after PVE only increased by 5% to 10% in patients with cirrhosis (7).

The rate of residual liver hyperplasia of PVL is comparable to that of PVE, and the completion rate of the second stage operation is higher than that of PVE (7), but there are also some shortcomings, including: (I) laparotomy is required, which is more traumatic and increases the surgical trauma; (II) because only the main trunk of the right portal vein was ligated, the communicating branches could also affect the effect of liver regeneration.

The efficiency of liver regeneration after ALPPS is higher than that of PVL and PVE, but there are also obvious disadvantages: (I) the mortality and complication rate of ALPPS is higher. Schnitzbauer *et al.* of Germany reported that the complication rate was as high as 64%, mainly due to bile leakage, severe infection and liver and kidney dysfunction (13). Schadde *et al.* analyzed 320 patients in 55 centers around the world, and the total mortality rate within 90 days was 8.8% (28/320) (14). Wang *et al.* reported that 45 patients in their single center had a mortality rate of 11.1% (5/45) within 90 days (15). (II) This operation could increase the risk of tumor dissemination during the operation.

Comprehensively comparing the above three methods, ALPPS has the highest liver proliferation efficiency, but it requires two large operations, and the complication rate and mortality rate are high. The main mechanism of ALPPS technology to promote residual liver regeneration includes blocking the communication branches of the portal vein between the liver parenchyma through the liver separation technology and ligation of the affected side portal vein, then all portal vein blood flow is promoted to the residual liver. Actually, ALPPS is one step more than PVL, which is to separate the liver parenchyma. Its purpose is to completely block the communicating branches between the reserved side and the resected side portal vein.

In addition to the above three most commonly used methods for increasing FLR, there are still hepatic vein deprivation and Y90 radiotherapy available internationally. Hepatic vein deprivation is a very new technique, with a limited number of reports and no standardized surgical process. Currently, there is still some controversy about its effect and long-term efficacy of tumor (16,17). Y90 also has the effect of reducing patient tumor and promoting contralateral liver tissue hyperplasia, but its effect of promoting FLR growth is not significant enough, and whether Y90 monotherapy could meet the requirements of transformation therapy remains to be further studied (18,19). Since Y90 radioembolization is still in the promotion stage in China, our hospital has not yet routinely carried out this treatment method.

Based on the mechanism of ALPPS promoting liver

hyperplasia, combined with the advantages of laparoscopic technology, we have designed this novel conversion strategy. On one hand, preoperative TACE could reduce tumor volume and inhibit tumor progression. It also contributes to hepatic ischemic preconditioning and facilitates the smooth implementation of subsequent steps. On the other hand, PVL and PVE are combined by laparoscopic technology, which is called laparoscopic PVL and terminal branches PVE combined with interventional therapy. The advantages of this method are as follows: (I) there was no need to use a spring coil, which could decrease medical cost and avoid ectopic embolism; (II) since the portal vein has been ligated, the blood flow in the portal vein is significantly reduced, which helps full embolization of the terminal branch of the portal vein, which is beneficial to promote the regeneration of the residual liver; (III) it can control the arterial blood supply of the tumor to prevent tumor progression during the waiting period and arterial compensation after portal embolization. In this case, the volume of the FLR increased by 49%, achieving an effect similar to ALPPS.

PVL combined with terminal branches PVE combines the advantages of ALPPS and PVE. On the one hand, it overcomes the insufficiency of the slow regeneration of the remaining liver after PVE. On the other hand, it simplifies the complicated ALPPS operation and effectively reduces postoperative mortality and complication rate. In addition, through the combined interventional treatment, on the basis of blocking portal blood supply, we could further reduce the tumor arterial blood supply. This could prevent tumor growth during the waiting process, and can also achieve the purpose of increasing side arterial flow, to better promote the growth of residual liver volume. This method is particularly suitable for laparoscopic surgery, which reduces the trauma of the first operation and is beneficial to the recovery of patients after surgery. For suitable cases, the second operation could also be completed under laparoscopy. Laparoscopic PVL combined with terminal branches PVE could improve the success rate and safety of the first operation and reduce the chance of tumor dissemination.

This study has the following limitations: (I) this is a retrospective study with small sample size, the findings may be biased and have a low level of evidence; (II) this study is a single arm study with no comparative group, the multi-center, large-scale clinical trial verification is needed in the future; (III) the support of hybrid operating room and interventional professional doctors are needed to perform this strategy.

Conclusions

In conclusion, we propose a new conversion strategy for HCC patients without enough FLR. This strategy has a relatively good effect of increasing the FLR, increases the chance of curative resection patients with HCC. The safety of this method is also good, and patients have relatively low rate of complications and mortality during the perioperative period.

Acknowledgments

Funding: This study was supported by Foshan Science and Technology Innovation Project (No. 2020001003307), The Guangdong Basic and Applied Basic Research Foundation (No. 2020B1515120031) and The Foshan Self-funded Science and Technology Innovation Projects (No. 2320001006090).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-507/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-507/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-507/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-507/coif). The 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). Informed consent was obtained from all the patients, and this study was approved by the ethics committee of The First People's Hospital of Foshan (No. FSYYY-EC-SOP-008-02.01-A09).

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Cite this article as: Yan Q, Wang FJ, He JW, Hu JY, Lai ECH, Chen HW. Trans-arterial chemo-emobilization (TACE) combined with laparoscopic portal vein ligation and terminal branches portal vein embolization for hepatocellular carcinoma: a novel conversion strategy. J Gastrointest Oncol 2024;15(5):2178-2186. doi: 10.21037/jgo-24-507