

# World Journal of *Gastroenterology*

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Fax: +1-925-2238243  
E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
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## Evolution of associating liver partition and portal vein ligation for staged hepatectomy: Simpler, safer and equally effective methods

Shu-You Peng, Xu-An Wang, Cong-Yun Huang, You-Yong Zhang, Jiang-Tao Li, De-Fei Hong, Xiu-Jun Cai

Shu-You Peng, Jiang-Tao Li, Department of Hepatobiliary and Pancreatic Surgery, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou 310009, Zhejiang Province, China

Xu-An Wang, Department of General Surgery, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai 200092, China

Cong-Yun Huang, Department of General Surgery, Yuebei People's Hospital Affiliated to Shantou University School of Medicine, Shantou 515063, Guangdong Province, China

You-Yong Zhang, Department of Radiology, Yuebei People's Hospital Affiliated to Shantou University School of Medicine, Shantou 515063, Guangdong Province, China

De-Fei Hong, Department of Hepatobiliary and Pancreatic Surgery, Zhejiang Provincial People's Hospital, Hangzhou 310009, Zhejiang Province, China

Xiu-Jun Cai, Department of Hepatobiliary and Pancreatic Surgery, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou 310016, Zhejiang Province, China

**Author contributions:** Peng SY and Wang XA contributed equally to this work; Peng SY and Wang XA wrote and revised the manuscript; Peng SY designed the TBPVE and TELPP approaches; Huang CY and Zhang YY performed the TBPVE and TACE and prepared the figures; all the authors participated in the TELPP operations except Zhang YY.

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**Correspondence to:** Shu-You Peng, MD, FACS(Hon), Department of Hepatobiliary and Pancreatic Surgery, The Second Affiliated Hospital of Zhejiang University School of Medicine, 88 Jiefang Road, Hangzhou 310009, Zhejiang Province, China. [zrwkpsy@zju.edu.cn](mailto:zrwkpsy@zju.edu.cn)  
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### Abstract

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been recently demonstrated as a method to induce rapid and extensive hypertrophy within a short time and has been employed for a variety of primary and metastatic liver tumors. However, controversies remain due to its high morbidity and mortality. To enable safer surgery, liver surgeons have searched for better technical modifications, such as partial ALPPS, mini-ALPPS, minimally invasive ALPPS, and Terminal branches portal vein Embolization Liver Partition for Planned hepatectomy (TELPP). It seems that TELPP is very promising, because it has the main advantage of ALPPS - the rapid increase of future liver remnant volume, but the morbidity and mortality are much lower because only one surgical operation is required.

**Key words:** Associating liver partition and portal vein ligation for staged hepatectomy; Terminal branches portal vein embolization; Terminal branches portal vein embolization liver partition for planned hepatectomy; Transarterial chemoembolization

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**Core tip:** Many technical modifications have been proposed for associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) due to its high morbidity and mortality. We described a new one, named Terminal branches portal vein Embolization Liver Partition for Planned hepatectomy, which uses a different method to interrupt the communicating portal vein branches, not by manipulation of the liver parenchyma but by the implementation of the embolization of terminal portal vein branches between both sides of the liver. It has the main advantage of ALPPS - the rapid increase of future liver remnant volume, but the morbidity and mortality are much lower.

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## INTRODUCTION

Associating liver partition and portal vein ligation (PVL) for staged hepatectomy (ALPPS) is a novel two-stage strategy for oncological liver surgery that was developed to induce future liver remnant (FLR) hypertrophy in patients with previously considered nonresectable liver tumors<sup>[1,2]</sup>. This great new approach was invented by chance by Schlitt in 2007 for a patient with hilar cholangiocarcinoma who was about to undergo right trisegmentectomy. Intraoperatively, it was found that the FLR would be insufficient. Then, he split the liver parenchyma along the falciform ligament to facilitate the left hepaticojunostomy for palliation together with PVL to induce hypertrophy of the left lateral lobe. Finally, he performed the second stage operation to resect the diseased liver because the computed tomography (CT) scan showed enormous hypertrophy of the FLR on postoperative day 8. The patient recovered from the operation<sup>[2]</sup>.

This technique was first reported by Baumgart *et al*<sup>[3]</sup> on a poster. In 2012, Schnitzbauer *et al*<sup>[1]</sup> published their experience with 25 cases performed in 5 German centers with a median FLR hypertrophy of 74% after a median time interval of 9 d. This value was markedly higher than that for portal vein occlusion

(PVE or PVL), which increases the FLR between 10% to 46% within 2 to 8 wk<sup>[4-6]</sup>. The article attracted significant interest from liver surgeons worldwide, and de Santibañes and Clavien<sup>[2]</sup> proposed the term "ALPPS" for this novel approach. In that article, the authors also revealed a hospital lethality of 12% and a 24% rate of biliary leakage requiring radiologic or endoscopic intervention. Then, an international registry was initiated to collect information from multiple centers worldwide from 2012 to monitor the feasibility and safety of ALPPS. The first analysis of 202 patients by Schadde *et al*<sup>[7]</sup> in January 2014 reported a perioperative 90-d mortality of 9% and an impressive hypertrophy of 80% within a median of 7 d. The high mortality rate has elicited an intense discussion and debate about the safety of ALPPS<sup>[8,9]</sup>.

## EVOLUTION OF ALPPS

Even though ALPPS is significantly characterized by increasing the insufficient remnant liver volume within a shorter interval for two-stage resection, much controversy has surrounded it due to its safety; for example, the reported remarkable morbidity was 16%-64% and the mortality rate was 12%-23%<sup>[10-13]</sup>. Barroso considered ALPPS as the last option, or the ultimate possibility to cure some patients; he thought that it was not ethical to propose this kind of operation to a patient without first proposing a PVE<sup>[14]</sup>. Thus, to reduce the perioperative mortality and morbidity rates, to achieve a long-term disease-free survival and to enable safer surgery, liver surgeons have searched for better technical modifications.

### General modifications of ALPPS

Based on their experimental model, Petrowsky *et al*<sup>[15]</sup> developed a technical modification, named p-ALPPS (partial ALPPS), to switch from full liver partition to partial transection (50%-80% of the transection surface). They compared 18 patients who underwent full transection with 6 patients who underwent 50% to 80% partition, and the results displayed a comparable degree of liver hypertrophy on postoperative day 11 with fewer severe complications (Dindo-Clavien grade  $\geq$  3b) and zero in-hospital mortality. Alvarez *et al*<sup>[16]</sup> confirmed the value of p-ALPPS by a prospectively multivariate analysis that included 21 patients who underwent partial partition. In addition, they defined partial partition as the level of the middle hepatic vein, whereas total partition as the vena cava. However, a partial partition during the first stage will challenge the second stage, as it requires longer liver parenchymal transection.

Hernandez-Alejandro *et al*<sup>[17]</sup> have cautioned that extensive dissection of the hepatoduodenal ligament increases the likelihood of segment 4 ischemia and potentially increases the risk of bile leakage and resulting septic complications. Consistent with this,

Tanaka *et al.*<sup>[18]</sup> considered that sepsis originating from the ischemic area produced by parenchymal division increases mortality, accounting for one-third of postoperative deaths. They described a modified ALPPS procedure that preserves the portal pedicles during parenchymal division to avoid producing an ischemic area. Five patients received this modification without mortality. Mean hypertrophy of the FLR was  $1.638 \pm 0.384$  a week after the first stage procedure.

de Santibañes *et al.*<sup>[19]</sup> proposed mini-ALPPS, which combined partial transection and intraoperative PVE without hilum dissection or liver mobilization during the first stage. They applied this technique in four patients with a result of 62.6% (range, 49%-79%) FLR hypertrophy in a median of 11 d (range, 6-15 d), and no one developed liver failure or major complications.

## SPECIAL MODIFICATIONS OF ALPPS

### **Avoidance of liver parenchymal division**

The prominent advantage of ALPPS is the rapid and extensive hypertrophy of FLR within a short time period; however, the morbidity rate and the in-hospital mortality rate are incredibly high, which constitutes a major concern. Of note, septic complications and bile leakage were observed in 20%-25% of patients. Obviously, bile leakage stems from the two raw surfaces of the split liver that are left behind in the abdominal cavity after the first stage operation. The bile leakage may result in septic complications. Therefore, the avoidance of liver parenchymal division is important. According to Alvarez *et al.*<sup>[12]</sup>, the mechanisms for rapid FLR hypertrophy might be because: (1) PVL creates a redistribution of hepatotrophic factors to the FLR, and this produces the active and necessary phenomenon of FLR hypertrophy; (2) liver partition causes local surgical trauma that per se might represent an important regeneration stimulus; (3) the impairment of bilateral cross-portal circulation allows a more dramatic increase in portal flow to the FLR; and (4) unlike one-stage major hepatectomies, in which the liver remnant has to address hyper flow and portal hypertension, in this technique the diseased arterIALIZED hemiliver allows the FLR to tolerate this hemodynamic stress, modulating the double hepatic vascular inflow.

Based on the third mechanism, liver parenchyma division can be avoided, so long as bilateral cross-portal circulation can be blocked by other methods. These methods are described below.

**Using a liver tourniquet:** In a 2013 case report, Robles Campos *et al.*<sup>[20]</sup> described a modification termed ALTPS (associating liver tourniquet and portal ligation for staged hepatectomy) with a hypertrophy of 150% of the FLR. Instead of an *in situ* split, a tourniquet was positioned around the liver following either Cantlie's line or to the right of the umbilical fissure for the first stage of ALPPS. This tourniquet

was then tied tightly enough to occlude all collateral vessels between the two lobes, which was confirmed by intraoperative ultrasound (IOUS). This modified approach might potentially decrease morbidity by decreasing technical complexity and shortening the operative time for the first stage of the operation.

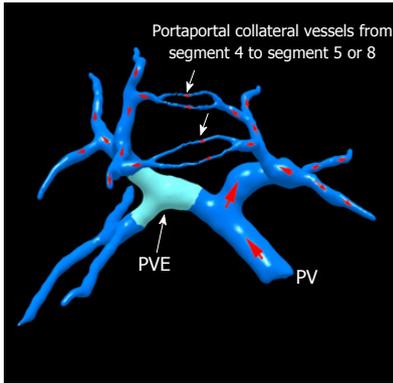
Cai *et al.*<sup>[21]</sup> adopted the execution of round-the-liver ligation to replace the *in situ* splitting of the liver, which could avoid postoperative bile leakage and might simplify the operation. The FLR volume increased by 37.9% according to the CT scan performed on day 10 after the first stage operation. The replacement of liver splitting by round-the-liver ligation could avoid biliary leakage, simplify the first stage operation and finally lead to a decrease in perioperative morbidity and mortality. Both the first and second stage operations were performed laparoscopically.

**Using microwave liver ablation:** Another new technique to avoid liver parenchymal division was presented by Gall *et al.*<sup>[22]</sup>. After right PVL, an inline radiofrequency ablation (RFA) probe was applied to the parenchyma instead of the *in situ* liver partition. The hypertrophy of the FLR was 62.3% at a mean interval of 21.8 d. In 2015, Gringeri *et al.*<sup>[23]</sup> described laparoscopic microwave ablation and PVL for staged hepatectomy (LAPS) on the future transection plane with a satisfactory hypertrophy of FLR and an easier second step in hepatocellular cancer (HCC) 10 d later. Compared with the traditional ALPPS, this technique may offer some advantages, such as an easier second operation due to the lack of adhesions and safer liver resection along the avascular groove.

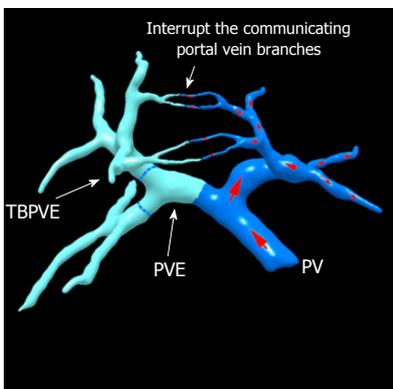
Hong *et al.*<sup>[24]</sup> presented a novel minimally invasive approach implementing percutaneous microwave ablation liver partition and portal vein embolization (PALPP) instead of the first step of ALPPS for rapid liver regeneration. The authors applied percutaneous microwave ablation (PMA) every 3 cm along the transection plane under ultrasonographic guidance until the formation of a necrotic groove from the inferior liver to the suprahepatic veins. The PMA line was positioned on the right side of the transection plane at a power of 60 W set as a 3-min ablation cycle. PVE was performed 3 d after PMA. Fourteen days later, a well-planned right trisectionectomy was performed. Three cases of HCC and 1 case of hilar cholangiocarcinoma were performed using this approach with a hypertrophic rate of 41.2%, which was similar to the results for HCC<sup>[25]</sup>. Hong's approach may have additional benefits. Tumor spread caused by ALPPS could be mitigated and intraoperative and postoperative bleeding along with bile leakage could be reduced as a result of microscopically coagulative necrosis.

### **Avoidance of two staged operations**

Original PVE only requires one operation, but the proliferative speed is too slow. However, the ALPPS



**Figure 1** Bilateral cross-portal circulation after portal vein embolization. Red arrows indicate blood flow to the S8 or S5 from the collateral vessels. PV: Portal vein; PVE: Portal vein embolization.

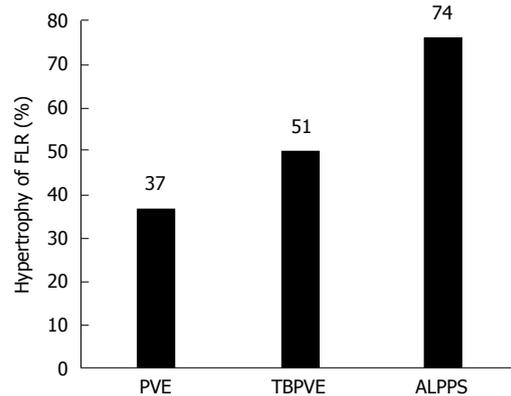


**Figure 2** Terminal branches portal vein embolization of S8 and S5. The communicating portal vein branches were interrupted without liver parenchyma division (red arrows indicate that blood flow to the S8 or S5 was interrupted, and blue dotted lines indicate the boundary between PVE and TBPVE). PV: Portal vein; PVE: Portal vein embolization; TBPVE: Terminal branches portal vein embolization.

and all modifications require two-stage operations with high morbidity and mortality rates. Is it possible to merge the concepts of ALPPS and PVE for designing a simpler and safer technique? It would be preferred to perform a single surgical operation rather than two to achieve the same therapeutic effect.

**TELPP:** The aforementioned special modifications of ALPPS to avoid liver parenchymal division have proven that the blockage of bilateral cross-portal circulation can promote FLR hypertrophy. Trying to search for a better way, we proposed terminal branches portal vein embolization (TBPVE) by applying an additional embolization agent on the endings of the portal vein system of S5, S8 or S4 (Figures 1 and 2).

TBPVE uses a different method to interrupt the communicating portal vein branches, not by manipulation of the liver parenchyma but rather by the implementation of the embolization of terminal portal vein branches between both sides of the liver. The mechanism of TBPVE is to separate the left and right sides of the liver by blocking communicating branches.



**Figure 3** Mean future liver remnant hypertrophy with portal vein embolization, terminal branches portal vein embolization, and associating liver partition and portal vein ligation for staged hepatectomy. FLR: Future liver remnant; PVE: Portal vein embolization; TBPVE: Terminal branches portal vein embolization; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

All blood in the portal vein on one side is diverted to the other side, and consequently the remnant liver proliferates at a speed comparable to that after ALPPS. There is no need to manipulate the liver parenchyma, such as the division of liver parenchyma, placing a liver tourniquet, or executing liver ablation. Thus, only a single surgical operation is needed. In the initial report, four patients who underwent this procedure followed by right hemi-hepatectomy two weeks later did not have mortality and severe morbidity. The mean hypertrophy was 52.2% (68.4%, 33.1%, 54.2% and 53.1%, respectively), which was similar to that with ALPPS<sup>[26,27]</sup>. Currently, TBPVE has been performed for 20 cases, and the mean rate of volume increase was 51% (Figure 3, unpublished data).

Based on these preliminary practices, TBPVE can effectively increase FLR similarly to ALPPS, but much less invasively. This indicates that TBPVE is simple, safe and effective and is able to avoid some disadvantages of ALPPS. It only needs one interventional manipulation and a single surgical operation to achieve a similar therapeutic effect to ALPPS. We propose naming it "Terminal branches portal vein Embolization Liver Partition for Planned hepatectomy (TELPP)". The efficacy and safety of this new technique is expected to be verified by a large-scale, multi-center study.

**TBPVE combined with TACE:** There is concern about tumor growth during the lag between PVE and surgical operations, as hepatic arterial flow might increase to promote the tumor growth. Kokudo *et al.*<sup>[28]</sup> described an increase of the tumor Ki-67 labeling index in intrahepatic metastases in the embolized liver after PVE. The same phenomenon was also noted with ALPPS. Fukami *et al.*<sup>[29]</sup> reported an increase in the Ki-67 labeling index from 60% at the first stage to 80% at the second stage by tumor biopsy results of the same liver lesion at both stages. TBPVE also raises the same concern, but not as strongly as PVE. This

problem was solved by performing TBPVE combined with TACE. When we used this method in four cases, the average rate of FLR volume increase was 68.6%, while the tumor mass shrank.

Recently, Chao *et al.*<sup>[30]</sup> found that lactic acidosis could effectively protect cancer cells against glucose starvation or deprivation and recruited 20 patients for a randomized trial to compare embolization alone with embolization plus bicarbonate treatment (TILA-TACE). The results showed that the tumors died more and patients survived longer if they received the bicarbonate. These data indicate that bicarbonate markedly enhances the anticancer activity of TACE. This therapy may be effective for patients with large tumors that are not amenable to surgery. Next, we would like to combine TBPVE with TILA-TACE to determine whether it could provide more benefit for patients with liver tumors previously considered nonresectable.

## CONCLUSION

ALPPS is a revolutionary two-stage surgical procedure for the resection of hepatic malignancies, which has attracted the attention of many hepato-biliary surgeons around the world. Many modifications have been proposed to reduce its high morbidity and mortality rates. So far, we found that TELPP, which applies and merges the concepts of ALPPS and PVE to perform TBPVE, may be a promising procedure. TBPVE combined with TILA-TACE is even better in view of the tumor growth problem during the lag before hepatectomy. Their technical feasibility, safety and oncological outcomes need to be verified further in a larger-scale and multi-center study.

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