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**Evolution of associating liver partition and portal vein ligation for staged hepatectomy: The simpler, safer and equally effective methods**

Peng SY *et al.* Evolution of ALPPS

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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 Planed hepatectomy. It seems that Terminal branches portal vein Embolization Liver Partition for Planed hepatectomy is very promising. 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 Planed hepatectomy; TBPVE combined with TACE

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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 Planed 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[1,2]. This great new approach was invented by chance by Schlitt in 2007 for a patient with hilar cholangiocarcinoma intended to undergo right trisecmentectomy. Intraoperatively, it was found that the FLR would be insufficient. Then, he split the liver parenchyma along the falciform ligament to facilitate the left hepaticojejunostomy as palliation together with PVL to induce hypertrophy of the left lateral lobe. Finally, he performed the second stage operation to respect the diseased liver because the CT scan showed enormous hypertrophy of the FLR on postoperative day 8. The patient recovered from the operation[2].

This technique was first reported by Baumgart *et al*[3] on a poster. In 2012, Schnitzbauer *et al*[1] published their experience of 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[4-6]. The article has generated significant interest from liver surgeons worldwide, and de Santibanes and Clavien proposed the term “ALPPS” (associating liver partition and portal vein ligation for staged hepatectomy) for this novel approach[2]. In that article, the authors also revealed a hospital lethality of 12% and biliary leakage requiring radiologic or endoscopic intervention of 24%. 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*[7] in January 2014 reported a perioperative 90-day mortality of 9% and an impressive hypertrophy of 80% within a median of 7 days. The high mortality rate has elicited an intense discussion and debate about the safety of ALPPS[8,9].

**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%[10-13]. 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[14]. Thus, to reduce the peri-operative mortality and morbidity rate, 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, Clavien *et al*[15] 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 at postoperative day 11 with fewer severe complications (Dindo-Clavien grade ≥ 3b) and zero in-hospital mortality. de Santibanes *et al*[16] 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*[17] 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. This agreed with Tanaka *et al*[18], who 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 future liver remnant was 1.638, 0.384 a week after the first-stage procedure.

de Santibanes *et al*[19] 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 4 patients with a result of 62.6% (range 49–79) FLR hypertrophy in a median of 11 days (range 6–15), 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 and constitute 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*[12], the mechanisms for rapid FLR hypertrophy might be: (1) PVL creates a redistribution of hepatotrophic factors to the FLR. This produces the active and necessary phenomenon of FLR hypertrophy; (2) liver partition, which causes local surgical trauma that per se might represent an important regeneration stimulus; (3) the impairment of bilateral cross-portal circulation, allowing 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, Pena Moral *et al*[20] 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 with intra-operative ultrasound (IOUS). This modified approach might potentially decrease morbidity by decreasing technical complexity and shortening operating times for the first stage of the operation.

Cai *et al*[21] 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 37.9% according to the CT scan performed on day 10 after the first-stage operation. The adoption of round-the-liver, which replaced liver splitting, could avoid biliary leakage and simplify the first-stage operation and finally led 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*[22]. After right portal vein ligation (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 days. In 2015, Gringeri *et al*[23] 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 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’s procedure. Hong *et al*[24] 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 author 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-minute ablation cycle. PVE was performed 3 days 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[25]. Hong’s approach may have additional benefits. Tumor spread caused by ALPPS could be mitigated and intra-operative 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 and all modifications require two-stage operations with a high morbidity and mortality rate. 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), applying an additional embolization agent on the endings of the portal vein system of S5, S8 or S4 (Figure 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. All blood in the portal vein on one side is diverted to the other side, and consequently the remnant liver proliferates at the speed of 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. The initial report of 4 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 ALPPS[26,27]. Currently, TBPVE has been performed for 20 cases, and the mean rate of volume increase was 51% (Figure 2, unpublished).

Based on these preliminary practices, TBPVE can effectively increase FLR similarly to ALPPS, but much less invasively. This shows 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 Planed 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*[28] described the increase of the tumor Ki-67 labeling index of intrahepatic metastases in the embolized liver after PVE. The same phenomenon was also noted with ALPPS. Kobayashi *et al*[29] 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 4 cases, the average rate of FLR volume increase was 68.6%, while the tumor mass shrank.

Recently, Chao *et al*[30] found that lactic acidosis could effectively protect cancer cells against glucose starvation or deprivation and recruited twenty patients for a randomized trial to compare just the embolization with the embolization with 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 liver tumors previously considered nonresectable.

**CONCLUSION**

ALPPS is a revolutionary two-stage surgical procedure for the resection of hepatic malignancies that has attracted the attention of many hepato-biliary surgeons around the world. Many modifications have been proposed to reduce its high morbidity and mortality rate. 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 outcome need to be verified further in a larger-scale and multi-center study.

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**Figure 1 Bilateral Cross-Portal Circulation after portal vein embolization (Red arrows: 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: blood flow to the S8 or S5 was interrupted**. PV: Portal Vein; PVE: Portal vein embolization; TBPVE: Terminal branches portal vein embolization; Blue Dotted Line: Boundary between PVE and TBPVE.



**Figure 3 Mean future liver remnant Hypertrophy of 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.