The Evolution of Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy

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ABSTRACT

Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy is a cutting-edge surgical technique for resection of hepatic malignancies that has piqued the interest of the international hepatobiliary community. Patients with insufficient future liver remnants, many of whom are considered unresectable via other methods, have the possibility of being cured with this treatment. The main issues; howbeit include, increased perioperative morbidity and mortality as well as both early and rapid disease recurrence. However, with continuous improving of patient selection, optimizing stage 2 operation times and refined operative techniques this has led to reduced morbidity and mortality rates. As for its usage, the most frequent indication is colorectal liver metastasis (CRLM); in which, the results in CRLM have shown higher resectability; however, it has a comparable complication rate to two-stage hepatectomy. Conversely, perihilar cholangiocarcinoma and hepatocellular carcinoma have terrible outcomes; although, with technical refinement and better patient selection good outcomes are achievable.

Herein, we summarized the current evidence based of the application of ALPPS in real-life practice, including the potential complications related to this procedure.

Keywords: ALPPS; Future liver remnant; hepatectomy (Siriraj Med J 2022; 74: 266-273)

INTRODUCTION

An insufficient future liver remnant is a factor excluding patients from curative intent liver resection, as the low hepatic functional reserve of the small, future liver remnant (FLR) can lead to post-hepatectomy liver failure (PHLF). Portal vein embolization (PVE) results in compensatory hypertrophy of FLR; however, the biggest drawback of PVE is insufficient FLR hypertrophy, or subsequent disease progression; which affects roughly 20% of patients.[1]

Recently, Two-stage hepatectomy (TSH) has been introduced for patients with bilateral multinodular colorectal liver metastases.[2] This can be used in conjunction with Portal vein occlusion (PVO); either portal vein ligation (PVL) or percutaneous PVE. The main idea being that the liver grows in the interval between sequential resection, and the risk of PHLF is presumably reduced due to this staged approach.[3,4] However, although TSH is well established, failure to proceed to stage 2 is reported as being a problem in up to one-third of patients.

Dr. Hans Schlitt discovered the Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy (ALPPS) by chance. He noticed a small liver remnant during an extended right hepatectomy for hilar cholangiocarcinoma. So, he decided to perform a hepaticojejunostomy and right PVL after parenchymal

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Received 2 December 2021 Revised 20 February 2022 Accepted 7 March 2022
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http://dx.doi.org/10.33192/Smj.2022.33

transection for enhancing exposure. Fortunately, computed tomography (CT) scanning revealed extensive hypertrophy of the remnant segments one week later. Hence, the right liver was subsequently removed.[5] ALPPS is based on the fast hypertrophy of remnant segments. It can enhance the remaining liver by up to 80% over an average duration of 1-2 weeks compared to 20-45% in 2-8 weeks in PVE patients.[6,7] The possible mechanism of rapid hypertrophy in ALPPS is based on the increase of portal flow in the disconnection of the interlobar perfusion, accompanied by the increased level of inflammatory cytokines that induce liver regeneration. The disadvantage is a high procedure-related morbidity and mortality rate of roughly 40% and 15%, respectively, mainly from liver failure and bile leakage.[8] As a result, the safety of ALPPS in comparison to standard techniques is still debatable.

Pathophysiology of liver regeneration in ALPPS

There are two proposed mechanisms for rapid hypertrophy after the first stage of ALPPS. Firstly, the parenchymal transection will not allow communication of interlobar collateral circulation. The portal flow can maximize the shearing force to the hepatocyte that causes the liver to regenerate. The later mechanism is based on the increased level of inflammatory mediators that drive liver regeneration.[9]

The disparity between the size and function of a remnant could explain the high risk of ALPPS complications. The regenerate hepatocyte shows edema and expansion, but is still partly immature within the first two weeks after the procedure, albeit from unknown causes.[10] Histologically, the hepatocyte has greater cell density, is smaller in size, brighter and has narrower sinusoidal compared to PVE.[11] In electron microscopy, the FLR area is frequently shown as being vacant in appearance. This is caused by hepatocytic cytoplasm filled with glycogen granules and fewer cytoplasmic organelles, lipofuscin granules. To date, all of these properties can be interpreted as immature cells.

Technical considerations (right trisectionectomy ALPPS)

The liver was examined with intraoperative ultrasonography to confirm the number and location of the tumor. The liver was fully mobilized, and the hepatoduodenal ligament was skeletonized. The right portal vein was ligated with non-absorbable suture material. The parenchymal transection was carried down along the falciform ligament (Fig 1). Most of the authors advocated for using a plastic bag for covering the deportalized liver, so as to control bile leakage. CT scanning was performed at 9 days on average, postoperatively. The right hepatic artery, right hepatic duct, right, and middle hepatic vein were then divided in the second stage operation.[5,12]

Modifications to the initial techniques

Bile duct ligation

Recent studies have suggested against routine bile duct ligation.[13,14] Many published reports have reported complications; such as, a higher rate of bile leakage, biloma formation and severe, dense adhesion at the porta hepatis during second stage operations. The previous hypothesis was that by increasing the biliary obstruction response in obstructed livers, right bile duct ligation could promote additional FLR hypertrophy.

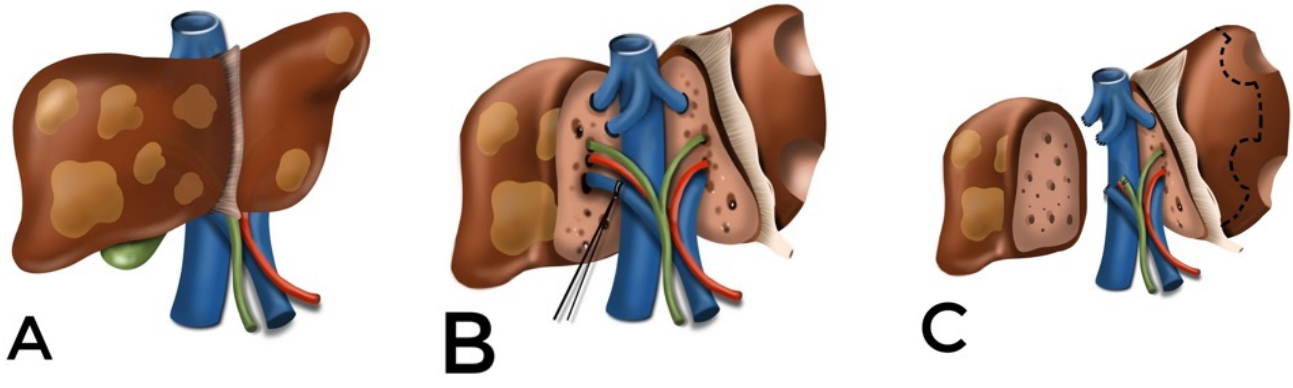

Fig 1. Schematic overview of Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy (right trisectionectomy). (A) The liver was occupied with multiple tumors on both sides. The potential procedure is right trisectionectomy with the lateral section as the future remnant liver. (B) In the first stage, complete parenchymal transection was carried out along the falciform ligament, the tumors in the remnant liver were removed, and the right portal vein was ligated. (C) The future liver remnant shows significant hypertrophy, and then the deportalized lobe was removed.

Preservation of the middle hepatic vein

The first ALPPS series mentions ligation of the middle hepatic vein during the first stage of the procedure[5] however, a recent study[13] discovered its relation with congestion of liver segments IV, V, VIII. This may result in decreased outflow, followed by a higher risk of ischemia and hepatic necrosis as well as subsequent bile leakage. The middle hepatic vein is now preserved as the venous outflow of segment IV, rather than being removed as previously reported, without compromising parenchymal hypertrophy. Most hepatobiliary surgeons currently use this method.[6]

Hybrid ALPPS (Non touch technique)

This modification aims to avoid manipulating the right lobe of the liver in order to improve tumor tissue handling and prevent hematologic malignancy spread.[13,15,16] The parenchymal transection is performed using an anterior approach, without mobilization, and the hepatoduodenal ligament is left intact. In the days following the operation, interventional radiology performs right PVE. At the second stage, there is less inflammation around the liver; according to reports. Nevertheless, some of the authors are against this idea, due to the inability to achieve optimal vascular control during a technically complex procedure; especially via an anterior approach.[14,15]

Partial ALPPS

This modified technique solely differs in the degree of liver partition. In contrast to conventional ALPPS, where parenchymal transection was complete, partial ALPPS transected only 50% to 80% of the parenchyma in stage I.[14] Anatomic outflow structures (hepatic veins), and/or tumor(s) lying inside or near the future transection line, determine the degree of partial transection. The main advantage of this modification in technique is that it limits the deleterious congestion of the excluded segments and segment IV necrosis, by preserving their outflow via the middle hepatic vein.[17,18] Partial ALPPS generates equivalent FLR hypertrophy to complete ALPPS, but with decreased morbidity and near-zero mortality.[16] However, Chan et al. demonstrated that complete ALPPS can cause rapid FLR hypertrophy more so than partial ALPPS, while having no impact on perioperative risks in chronic liver disease.[19] In the meta-analysis by Wu et al, they compared partial and complete ALPPS and showed that FLR hypertrophy and time intervals between stages were not substantially different for both techniques.[20] Although, the post-operative complication rate was significantly lower in partial ALPPS.

Mini-ALPPS

Mini-ALPPS simplifies first stage hepatectomy, by using a partial parenchymal transection technique and intraoperative portal vein embolization, without hilar dissection or liver mobilization. This approach allows for an accelerated FLR hypertrophy to be obtained at a mean of 63% within 11 days.[19] This is similar to that reported for classic ALPPS; but without the high rate of mortality and morbidity.[5,6]

Associating Liver Tourniquet and Portal Ligation for Staged Hepatectomy

With this method, a tourniquet is used to replace the completion of the parenchymal transection, this reduces the complexity and time required in the first stage of the operation.[21] A thick suture material is applied around the liver in the deep sulcus of the parenchymal transection (an extra-glissonian approach). Then the tourniquet is subsequently tightened to completely obstruct all interlobar collateral circulation.

Radiofrequency assisted liver partition

This is an application of radiofrequency ablation to the parenchyma, after right PVL at the site of demarcation. The hypertrophic rate is increased by up to 62% over a mean interval of 22 days, according to the study, and that it also avoids the complications of liver partition.[22]

ALPPS outcome

Primary outcomes

The studies that investigated the efficacy of ALPPS have consistently revealed that ALPPS causes hypertrophy of 60-90%, with the average duration of the stage being 9-14 days (Table 1). Most of the cases (95-100%) that complete the first stage could be undergoing a later stage.[5,6,15,23,24] The international ALPPS registry consists of 141 (70%) colorectal liver metastasis (CRLM) patients among 202 patients.[25] Within 7 days, the median initial standardized future liver remnant of 21% grew by 80%, and ninety-day mortality was 9%. Severe complications occurred in 27% of patients. Red blood cell transfusion, an operative time of more than 300 minutes, patient ages being greater than 60 years, and non-CRLM were all independent risks for severe complications. Additionally, the registry shows that many factors directly affect the rate of liver hypertrophy; such as, age, intermittent Pringle maneuver, and abnormal parenchyma.[25]

According to meta-analysis,[26] ALPPS seems to be more effective than the two-stage approach in causing remnant hypertrophy, with significantly higher resection

TABLE 1. Success rate and outcome of Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy compare with two-staged hepatectomy.

Author (reference)	Year	Primary tumor (N)			FLR volume increment (%)		Drop-out rate after first stage (%)		Morbidity*/ mortality (%)
		CRLM	HCC	CCA	ALPPS	TSH	ALPPS	TSH	
Schnitzbauer[5]	2012	14	3	4	74	n/a	n/a	n/a	64/12
Shindoh J[8]	2013	14	3	4	70	62	n/a	28	40/12
Schadde E[25]	2014	141	17	19	80	n/a	2	n/a	27/9
Schadde E[6]	2015	228	32	27	90	n/a	2	n/a	14/9
Sandstrom[31]	2018	97	-	-	68	36	8	43	43/8
Wang Z[36]	2020	-	45	-	57	n/a	9	n/a	12/11
Chan A[37]	2021	-	46	-	49	38	2	32	21/6.5

Abbreviations: CRLM; Colorectal Liver Metastasis, HCC; Hepatocellular carcinoma, CCA; Cholangiocarcinoma, FLR; Future liver remnant, ALPPS; Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy, TSH; two-stage hepatectomy
* Clavien-Dindo grade ≥ IIIB
n/a: non-available

rates of approximately 92-100%.[25–28] Additionally, there is a shorter time interval of 1-2 weeks vs. 20-45% in 2-8 weeks following PVE. Furthermore, prolonged periods between stages in TSH has caused up to 30% of patients to be ineligible for a final hepatectomy, due to disease progression.[10,29,30] At the same time, ALPPS faces the problem of most candidates having a higher risk for micrometastasis in FLR after a second stage operation. Additionally, there is an argument concerning the hypertrophic liver, in regards to cellular swelling or complete functioning regeneration, and that liver hypertrophy in such a short period of time may not ensure its functional capacity.[9] In conclusion, despite ALPPS having a greater resectability rate, there is no significant difference in disease free survival between ALPPS and TSH.

Morbidity and mortality

The major obstacle of the procedure is the significant rate of morbidity and mortality. The largest study, 202 patients, cited major morbidity of 28% and mortality of 9%.[6,15,25] Although, the reported mortality rate is variable, the high complication rate is may have occurred from the small sample size of the study. A German study revealed a 12 percent 90-day death rate, triggering a fierce debate among international experts;[5] surgical exploration, right portal vein ligation (PVL additionally, other small studies found significantly higher rates; ranging from 22-29%. Conversely, there have been no 90-day mortalities recorded across multiple centers.[13,15,25]

Comparison between ALPPS and Two-stage hepatectomy.

The retrospective comparative analysis of 140 patients undergoing PVE to the 25 patients undergoing ALPPS showed that the rates of hypertrophy were similar in both groups: 70% in the ALPPS group and 60% in the PVE group.[8] Overall, there was no significant difference in major morbidity between the two groups (40% ALPPS versus 30% PVE). However, for other complications ALPPS had significantly higher rates than PVE in all causes; bile leak (24% versus 6%), re-laparotomy (30% versus 3%) and sepsis (20% versus 0%); but was no significantly higher in liver-related mortality (12% versus 6%).

Data from the retrospective multicenter study showed a trend towards higher morbidity and mortality associated with ALPPS compared with PVE. The 90-day mortality was 15% versus 6%, and post-hepatectomy liver failure was 13% versus 9% for the ALPPS versus the PVE group, respectively. Moreover, patients in the

ALPPS group achieved more completion of resection (83% versus 66%); however, the recurrence at one year was comparable (54% versus 52%).[25]

In contrast to Aloia et al, the PVE group had just a 34% increase in FLR compared to a 77% gain in the ALPPS group.[28] The LIGRO was a landmark randomized controlled trial that compared the resection rate between ALPPS and TSH in CRLM patients. This study demonstrated that ALPPS could offer a higher resection rate compared to TSH, 92% to 57%, respectively, with comparable surgical margins, complications, and short-term mortality.[31]

A recent systematic review and meta-analysis of ALPPS versus traditional staged hepatectomy, in 2019,[7] found that ALPPS increased FLR more than PVE and TSH. However, the results of the study are limited due to the high heterogeneity among the studies. As for overall mortality and morbidity, the higher trend is on the side of ALPPS over PVE/TSH; morbidity 30% and 26%, respectively, without heterogeneity; mortality 10% and 4% consequently, without heterogeneity. The feasible rate of stage 2 after ALPPS and PVE were 94% versus 63%, respectively, which is the same as between ALPPS and TSH, 95% versus 72%, respectively.

ALPPS in CRLM

In the first international registry,[6] the 90-day postoperative mortality among all patients who underwent ALPPS was 9%. For patients with CRLM, the 2-year overall survival (OS) and disease-free survival (DFS) were 62% and 41%, respectively. Patients with CRLM who were younger than 60 years of age had a better chance of survival than patients with other malignancies. A separate analysis of the international ALPPS registry included 228 patients with CRLM, which comprised of 72% of the study population. In this report, the 90-day mortality was 5%. The leading cause of mortality was liver-related, for which it was recommended by the authors to evaluate the patients underlying condition, using the model of end-stage liver disease, and the international study group for liver surgery criteria, so as to discriminate against higher or lower risk.[27]

Some of the suggested approaches to improve ALPPS outcome include stratification of patients for developed liver failure following first stage hepatectomy, achieving expertise in the learning curve, refinement in patient selection, modifications to the original ALPPS procedure to reduce liver traumatization, interval chemotherapy, a shorter time off chemotherapy, and preservation of segment IV.[9] The objective of oncologic liver surgery is to achieve a tumor-free margin. In there meta-analysis, Margonis et al,[29] found that a margin of >1 mm was related with better overall survival, and a margin of >1 cm was even associated with better DFS. As a result, a better oncologic outcome may even justify the removal of significant volumes of parenchyma. Furthermore, regarding the numbers and sizes of metastases remaining in the FLR, full tumor clearance of the FLR during the first stage is crucial for any two-stage strategy. These traditional markers; numbers and sizes of metastases as well as intensity of oncologic pretreatment area are important prognostic factors. KRAS mutation, which has been linked to poor survival, and TP53 mutation have both been linked to a higher chance of tumor relapse in recent studies.[30]

Hence, analysis by Schnitzbauer et al,[32] assumed that there is a tendency for potential overuse of ALPPS. Additionally, the role of major hepatectomy in CRLM has become less, due to effective down-sizing of chemotherapy being available. In this case, ALPPS must be viewed as a last resort at the very end of the therapeutic spectrum for CRLM.

ALPPS in Hepatocellular carcinoma (HCC)

The ALPPS registry's initial report, which included 17 patients with HCC, and the second, which included 32 patients with HCC, reported 90-day mortality rates of 12% and 13%, respectively.[6,25] These results appeared to be the consequence of both an early learning curve and a typically increased mortality of liver resection in altered liver parenchyma. More devastating was when the first major analysis from the ALPPS registry, with 35 ALPPS for intermediate-stage tumor, revealed a 90-day mortality of 30%.[33] However, a thorough examination revealed that ALPPS had been employed with broad inclusion criteria and in an undifferentiated manner. Fortunately, after careful selection, using the ALPPS technique in a good patient candidate with HCC (Child A cirrhosis, FLR volume > 30%, an indocyanine green clearance rate at 15 minutes <20%, platelet count > 100,000/μL and no complete right portal vein thrombosis), led to a decrease in mortality of 7% and 0%.[23,34,35] A recent study, from Wang et al, investigated their outcomes of conventional ALPPS in 45 HCC patients.[36] The results showed that the patients who received ALPPS had similar effects to those who underwent one-stage hepatectomy,; with 1- and 3-year OS rates of 64% and 60% and 1- and 3-year DFS rates of 48% and 44%. Furthermore, the results were far superior to those who received transarterial chemoembolization. Recently, Chan et al. investigated the role of ALPPS for hepatitis-related HCC. The study shows ALPPS induced FLR volume increment by 48.8%, without difference in morbidity and mortality compared

to PVE. Although, over 56.5% of patients that complete stage 2 had cirrhosis.[37]

ALPPS in cholangiocarcinoma

From the beginning, ALPPS was firstly used in a case of hilar cholangiocarcinoma, even so, the latest data reveals the highest perioperative complication risks among all indicated diseases. The 90-day-mortality for intrahepatic cholangiocarcinoma from the ALPPS registry is about 13%.[6] The risk of perioperative complications is higher in perihilar cholangiocarcinoma (PHC), most likely from post first stage parenchymal necrosis, possibly infected bile, and biliary leakage. A matched case study that compared data from the ALPPS registry to data on PVE and right trisectionectomy for PHC found that perioperative mortality was as high as 48% in the ALPPS group versus 24% in the matched group.[38] These results led to unacceptable arguments over whether it is a homicidal choice of treatment or not. However, from a closer viewpoint, ALPPS in the research was performed with the intention to improve resectability, by rapidly increasing FLR; but at the same time some principles of surgery for PHC were neglected. For example; performing the 1st stage operation in the presence of infection and inflammation by conventional ALPPS; thereby causing a higher risk of biliary leakage. Conversely, new techniques; such as: "Mini-ALPPS" and "Hybrid ALPPS", were introduced. Both strategies aim to achieve appropriate FLR growth in the shortest period possible, and both prevent hilar dissection during the first stage. As a result, in PHC patients, ALPPS should not be deemed a categorical contraindication.

Authors opinions

After the initial outcome of ALPPS demonstrated the dramatic increment of FLR, this procedure became famous among the hepatobiliary surgery community. However, many patients have been through this procedure without proper indication, which has lead to avoidable complications. Even with the international ALPPS registry results, the 90-day mortality was much higher than conventional hepatectomy.[6]

The authors suggest that the following issue should be considered before selecting a patient for ALPPS.

1. For CRLM: the patient should receive episodes of systemic chemotherapy, with or without targeted therapy. Good response liver metastasis could omit the need for this risky procedure. ALPPS should only be used as a last measure in the treatment of CRLM.[32]
2. The CRLM patients who progress while on systemic therapy are poor candidates for ALPPS.
3. After stage 1, preoperative liver evaluation is crucial. Both quantitative and qualitative assessments are essential. The second stage should be terminated, or postponed for any patient that has good FLR increase but impaired function. There are some discrepancies between the increased volume and the remnant›s function because most of the regenerated hepatocyte is still partly immature.[10]
4. In chronic viral hepatitis or cirrhosis there is scant evidence of ALPPS; therefore, the surgeon should select the most suitable patients for ALPPS.
5. Patients with cholangiocarcinoma should avoid ALPPS. ALPPS in cholangiocarcinoma had the highest risk of perioperative complication among all indicated diseases. The 90-day-mortality for intrahepatic cholangiocarcinoma is high as 13%, and might be higher for perihilar cholangiocarcinoma.[6]

CONCLUSION

ALPPS is one of the strategies to overcome inadequate future liver remnants. Perioperative complications are the main concern for ALPPS, because the tremendous volume increment within 1-2 weeks is not well correlated with the function of the remnant liver. As early results from the ALPPS registry have shown, inappropriate patient selection resulted in a high risk of PHLF and postoperative mortality. Proper patient selection coupled with a satisfactory pre-and interstage liver assessment could improve outcomes; especially for CRLM, which has comparable results to TSH.

ACKNOWLEDGEMENT

The authors would like to thank Woralux Phusoongnern, M.D., FRCNST, for the illustrations.

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