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An updated systematic review of the evolution of ALPPS and evaluation of its advantages and disadvantages in accordance with current evidence

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Abstract

The main obstacle to achieving an R0 resection after a major hepatectomy is inability to preserve an adequate future liver remnant (FLR) to avoid postoperative liver failure (PLF). Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a novel technique for resecting tumors that were previously considered unresectable, and this technique results in a vast increase in the volume of the FLR in a short period of time. However, this technique continues to provoke heated debate because of its high mortality and morbidity.

The evolution of ALPPS and its advantages and disadvantages have been systematically reviewed and evaluated in accordance with current evidence. Electronic databases (PubMed and Medline) were searched for potentially relevant articles from January 2007 to January 2016.

ALPPS has evolved into various modified forms. Some of these modified techniques have reduced the difficulty of the procedure and enhanced its safety. Current evidence indicates that the advantages of ALPPS are rapid hypertrophy of the FLR, the feasibility of the procedure, and a higher rate of R0 resection in comparison to other techniques. However, ALPPS is associated with worse major complications, more deaths, and early tumor recurrence.

Hepatobiliary surgeons should carefully consider whether to perform ALPPS. Some modified forms of ALPPS have reduced the mortality and morbidity of the procedure, but they cannot be recommended over the original procedure currently. Portal vein embolization (PVE) is still the procedure of choice for patients with a tumor-free FLR, and ALPPS could be used as a salvage procedure when PVE fails. More persuasive evidence needs to be assembled to determine whether ALPPS or two-stage hepatectomy (TSH) is better for patients with a tumor involving the FLR. Evidence with regard to long-term oncological outcomes is still limited. More meticulous comparative studies and studies of the 5-year survival rate of ALPPS could ultimately help to determine the usefulness of ALPPS. Indications and patient selection for the procedure need to be determined.

Abbreviations: ALPPS = associating liver partition and portal vein ligation for staged hepatectomy, FLR = future liver remnant, HCC = hepatocellular carcinoma, ISS = in situ splitting, PLF = postoperative liver failure, PVE = portal vein embolization, PVL = portal vein ligation, TSH= two-stage hepatectomy.

Keywords: ALPPS, portal vein embolization, portal vein ligation, two-stage hepatectomy

1. Introduction

The main curative treatment for liver cancer is an R0 resection, and an R0 resection provides hope for patients with a large primary cancer of the liver or extensive hepatic metastases. Postoperative liver failure (PLF) is the most common cause of mortality after an extended hepatectomy,[1] so PLF is the biggest obstacle faced by hepatobiliary surgeons. Thus, the main obstacle to improving the rate of R0 resection after a major hepatectomy is inability to preserve an adequate future liver remnant (FLR) to avoid PLF. Large studies are being conducted and approaches are being devised to make major hepatectomy safer.

Whether a hepatic resection is performed generally depends on preoperative liver function, the status of the liver, and the volume of the FLR. For people with a normal liver, an FLR ≥25% of total liver volume is adequate to avoid liver insufficiency. Patients with chronic liver disease but without cirrhosis usually require an FLR of at least 30% while patients with cirrhosis but without portal hypertension require an FLR of at least 40%.[2,3] The functional state of the liver does not usually change as a result of a prolonged viral infection or chemotherapy-related injury. Therefore, the procedure to perform is decided on the basis of the status of the liver according to an examination or biopsy, a precise assessment of liver function (e.g. ICG clearance or 99mTc-GSA),[4] and an adequate volume of the FLR as estimated with advanced imaging.[5] Over the past 3 decades, surgeons have endeavored to induce hypertrophy of a small FLR, particularly in patients with hepatocellular carcinoma (HCC) who were not eligible for

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liver resection.[6–8] Makuuchi et al[9] first described portal vein embolization (PVE) in 1990, which they used to induce hypertrophy of the left side of the liver to increase the safety of a major hepatectomy for treatment of hilar cholangiocarcinoma. Later, a 2-stage hepatectomy (TSH) was described by Adam et al[10] as a means to achieve an R0 resection in patients with bilobar liver tumors. An alternative technique, portal vein ligation (PVL), triggers a similar or better regenerative response than PVE.[11,12] PVE and PVL are now routinely used in TSH to improve the rate of a successful R0 resection.[2,13,14] Although portal occlusion (PVE or PVL) can increase the volume of the FLR by up to 40% within 3 to 8 weeks, the second stage of the procedure was not always performed.[15,16] In a study by Shindoh et al,[17] 27.8% of patients dropped out. Tsai et al[18] reported a drop-out rate of 22%. Generally, the second stage of surgery is canceled due to disease progression in a short period of time, insufficient liver regeneration, or comorbidities.

In 2012, Schnitzbauer et al described a novel approach: associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). This new surgery resulted in a 74% increase in the volume of the liver remnant in a mean period of 9 days.[19] This procedure vastly reduced the interval between the 2 surgeries, resulting in a completion rate of 100%. However, this procedure was associated with a morbidity rate as high as 68% and a mortality rate as high as 14%. The study by Schnitzbauer et al triggered a large number of letters to the editor from some of the most talented liver surgeons around the world.[20–24] Three years have passed since ALPPS debuted and much progress has been made, but this procedure continues to provoke heated controversy. Thus, we conduct a systematic review regarding the evolution of ALPPS and evaluation of its advantages and disadvantages in accordance with current evidence.

2. Methods

2.1. Search strategy

Electronic databases (PubMed and Medline) were searched for potentially relevant articles from January 2007 to January 2016 published in English. The search strategy was: ["ALPPS"(Title/Abstract) OR "associating liver partition and portal vein ligation for staged hepatectomy"(Title/Abstract)] OR "in situ split"(Title/Abstract). Some of the citations listed in the references of articles were searched manually.

Titles, abstracts, and full-text articles were screened by 2 authors (Y-LC and P-PS). Any discrepancies were resolved in consultation with a third author (WT).

2.2. Inclusion and exclusion criteria

To ascertain the complete history and evolution of ALPPS, broad inclusion criteria were used. Studies were required to meet the following criteria: no restrictions on study design were imposed; all original articles, case reports, letters, meta-analyses, and reviews regarding ALPPS were included, the language of publication was restricted to English, and no restrictions on the type of tumor were imposed; benign and malignant tumors were included. Articles were excluded if they failed to fulfill any of these criteria.

2.3. Data extraction

To better evaluate the advantages and disadvantages of ALPPS, all of the reviewers (Y-LC, P-PS, WT, and N-SC) extracted original studies from the identified articles. A case series required more than 6 cases for sufficient strength of evidence. At a minimum, a study had to include a description of the procedure, the procedure's completion rate, the rate of an R0 resection, and morbidity and mortality. If 2 studies were found to refer to the same data, the publication that provided more specific data was included. Eligible studies were included in a qualitative synthesis and categorized into levels of evidence in accordance with levels defined by the Oxford Center for Evidence-based Medicine (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/). The validity of studies was assessed by 2 authors (N-SC and WT) who independently assessed the risk of bias as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (http://www.cochrane.org/esources/handbook/). The current work was a systematic review, so ethical approval was not necessary.

3. Results

Duplicate papers were excluded, resulting in a total of 117 articles regarding ALPPS. Forty-one original studies were identified. Case series $\leq$6 cases (n=18), letters (n=5), and duplicate studies (n=2) were excluded. Ultimately, 16 studies were identified and qualitatively analyzed, as shown in Table 1.[19,25–39] The level of evidence in these studies was low: 1 study was level 3a, 2 studies were level 3b, and the remaining studies were level 4. There were no randomized controlled trials (RCTs) and retrospective studies presented varied or insufficient data. Therefore, a meta-analysis was not performed. Fifteen studies had a high risk of bias, and only 1 study conducted by the ALPPS Registry had a moderate risk of bias. The primary form of bias was publication bias.

3.1. Timeline for the development of ALPPS

The origins of ALPPS are somewhat dramatic. Dr Hans Schlitt first performed "ALPPS" in Regensburg, Germany in 2007. He had planned to perform an extended right hepatectomy, but during surgery he determined that the future cholestatic liver remnant was too small to sustain the patient, so he quickly made a surprising decision. Schlitt performed an in situ split of the liver parenchyma along the falciform ligament for optimal positioning of a hepaticojejunostomy and he ligated the right portal vein to induce the hypertrophy of segments II to III. Unexpectedly, the left liver grew substantially according to a CT scan on postoperative day 8. Schlitt[40] then decided to remove the diseased liver and did so successfully. This novel approach was formally described later in 2011 by Dr Hauke Lang, from Mazin, Germany, in a series of 3 cases on a poster presented during the Ninth European-African Hepato-Pancreatico-Biliary Association Congress in Cape Town, South Africa.[41] The same year, a group of surgeons in Argentina adopted this new technique and shared their initial experiences.[42,43] Then the surgery group led by Schlitt formally presented "ALPPS" in a case series of 25 patients published in the *Ann Surg*.[19] Santibanes and Clavien[40] cited the need to create a self-explanatory and readily acceptable name for this procedure, so they proposed the acronym "ALPPS." Since then, ALPPS has represented both a major contribution to the field of liver surgery and an instant source of controversy. An international ALPPS registry (http://www.alpps.net/) was created to monitor the results and evolution of the procedure.[44] To date, a total of 553 cases from 84 centers around the world have been registered with the ALPPS registry.

Table 1

Summary of reported outcomes of ALPPS.

Surgical approach (study type)	Tumor type (n)	Evidence level	Patients (n)	Age (yr)	Volume increase (%)	Interval (days)	Preop chemo (%)	Completion (%)	R0 resection (%)	Overall morbidity (%)	In-hospital mortality (%)	OS (%)	Recurrent (%)	Ref.
Conventional ALPPS (multicenter)	CRLM (14), HCC (3), Hilar CC (2), ICC (2), GBC (1), MEH (1), NCRLM (2)	4	25	63	74	9	48	100	96	64	12	6-months (86)	NR	Schinitzbauer et al[19]
Conventional ALPPS (single-center)	CRLM (7), HCC (1), Hilar CC (1), NCRLM (1)	4	10	52	82	7	60	100	100	40	0	NR	20	Sala et al[26]
Conventional ALPPS (multicenter)	CRLM (32), HCC (1), Hilar CC (3), Benign (1), SA (2)	4	39	57	83	14	NR	95	100	59	13	NR	NR	Torres et al[27]
Conventional ALPPS (single-center)	CRLM (7)	4	7	66	65	13	29	100	100	86	0	1 year (71)	86	Oldhafer et al[28]
Conventional ALPPS (single-center)	CRLM (7), ICC (3), Hilar CC (3)	4	9	67	87	13	30	100	100	66	22	NR	NR	Li et al[29]
Conventional ALPPS (single-center)	CRLM (5), HCC (1), Hilar CC (5), ICC (4)	4	15	67	87	13	33	100	87	67	29	NR	40	Nadalin et al[30]
ALTPS (single-center)	CRLM (17), HCC (1) NCRLM (4)	4	22	65	61	7	68	100	100	63	9	1 year (91)	5	Robles et al 2014[25]
Conventional ALPPS (multi-center)	CRLM (26), HCC (3), Hilar CC (4), ICC (8), NCRLM (7)	3b	48	57	77	7	58	100	83	73	15	NR	NR	Schadde et al[31]
Conventional ALPPS (multicenter)	CRLM (141), HCC (17), Hilar CC (11), ICC (8), GBC (6), NCRLM (19)	3a	202	60	86	10	NR	98	91	IIIA (40) IIIB (28)†	9	1 year (73) 2 years (59)	NR	Schadde et al 2014[32]
Conventional ALPPS (single-center)*	CRLM (14)	4	14	57	93	8	100	100	86	36	0	9-months (100)	14	Hernandez-Alejandro et al[33]
Conventional ALPPS (multicenter)	CRLM (12)	4	12	59	47	11	75	100	100	83	8.3	1 year (92)	27	Ratti et al[34]
Conventional ALPPS (multicenter)	CRLM (50), HCC (3), Hilar CC (3), GBC (4), NCRLM (4)	3b	62	59	48	8	82.3	95	NR	80.6	12.9	NR	NR	Truant et al[35]
Conventional ALPPS (single-center)	CRLM (10), NCRLM (1)	4	11	68	54	7	100	100	0	First (18), Second (46)‡	9	NR	NR	Tanaka et al[36]
Conventional ALPPS or partial ALPPS (single-center)	CRLM (19), HCC (3), Hilar CC (1), ICC (1), NCRLM (6)	4	30	57	90	6	60	97	93.1	53	6.6	1 year (78) 2 years (63)	40	Alvarez et al[37]
Conventional ALPPS (single-center)	CRLM (9), HCC (1), Hilar CC (1), ICC (2), NCRLM (3),	4	16	61	86	9	43.7	100	100	64	12.5	3 years (49)	56	Lang et al[38]
Anterior approach for ALPPS (single-center)	HCC (13)	4	13	62	53	8	NR	100	100	15.3	7.7	NR	NR	Chan et al[39]

ALTPS = tourniquet placed in the umbilical fissure and right portal vein occlusion, Chemo = chemotherapy, CRLM = colorectal liver metastases, GBC = gallbladder cancer, HCC = hepatocellular carcinoma, Hilar CC = hilar cholangiocarcinoma, ICC = intrahepatic cholangiocarcinoma, NCRLM = noncolorectal liver metastases, NR = not reported, OS = overall survival, Preop = preoperative, SA = sarcoma.

* Preserved venous outflow and arterial inflow in segment 4.

† Only reported the number of complications (Clavien–Dindo grade ≥IIIA and IIIB).

‡ Only reported the number of complications after the first operation and the second operation.

3.2. Evolution of ALPPS

In its original form, ALPPS is a 2-stage extended right hepatectomy or right trisectionectomy (Fig. 1A). Stage 1 includes surgical exploration, right PVL, and in situ splitting (ISS) of the liver parenchyma along the right side of the falciform ligament. All portal, arterial, and biliary segment IV branches are identified along the right rim of the round ligament, divided, and are either clipped with metal clips or oversewn. Biliary and arterial structures and venous drainage of the right liver are retained. Stage 2 involves removing the right-extended lobe and ligating the right hepatic artery, right bile duct, and hepatic vein.[19]

ALPPS has now evolved into various forms devised by different surgeons around the world.

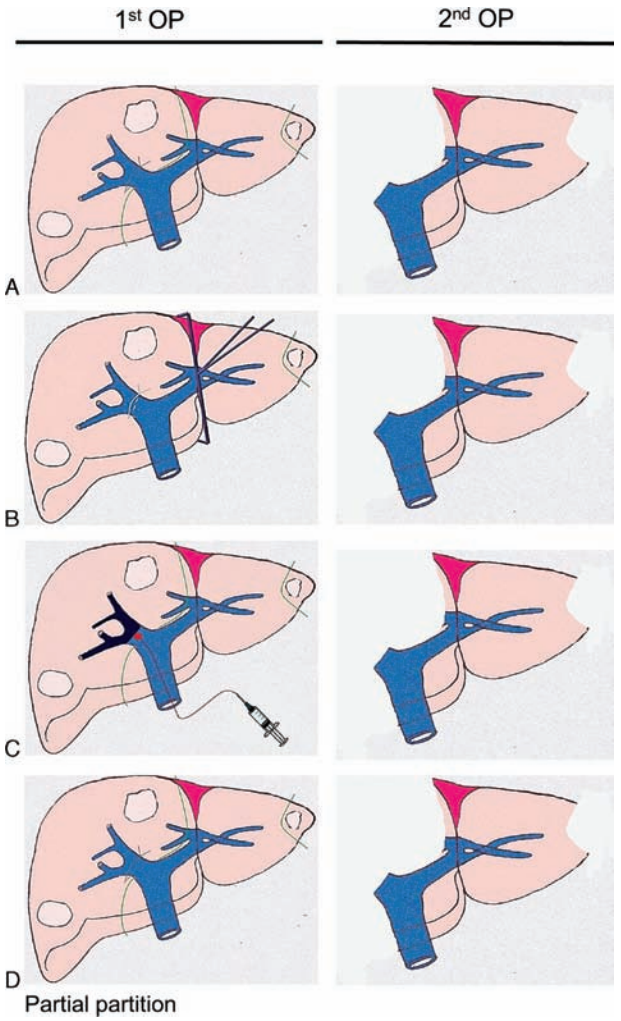

Figure 1. ALPPS and modified ALPPS (green: line for resection and splitting of the liver; gray: Ligature thread). A, Conventional ALPPS: first surgery: right PVL and in situ splitting of the liver parenchyma (with or without local resection). Second surgery: hepatectomy. B, ALTPS: first surgery: right PVL and placement of a tourniquet on the umbilical ligament, instead of in situ splitting of the liver parenchyma (with or without local resection). Second surgery: hepatectomy. C, Hybrid ALPPS: first surgery: in situ splitting of the liver parenchyma via an "anterior approach" (with or without local resection) and right PVE one day later. Second surgery: hepatectomy. D, p-ALPPS: first surgery: right PVL and partial partition to the level of the middle hepatic vein (with or without local resection). Second surgery: hepatectomy.

3.3. ALPPS in right hepatectomy

The Argentinian group first used ALPPS in a right hepatectomy. The original procedure was modified by changing the splitting line from the falciform ligament to Cantlie's line. Satisfactory results were achieved.[43]

3.4. Laparoscopic ALPPS

Soon afterward, Machado et al used laparoscopy during the first stage of the procedure. They indicated that laparoscopic ALPPS might prevent firm adhesions, allowing an easier second stage.[45,46] Totally laparoscopic ALPPS was performed by different institutions over the next 3 years, and 4 procedures have been described in the current literature.[47–49] A modified form of laparoscopic ALPPS, termed laparoscopic microwave ablation and portal vein ligation for staged hepatectomy (LAPS), has recently been described. LAPS has 2 steps: In step 1, laparoscopic right portal vein occlusion is performed with microwave ablation on the future transection plane and in the FLR, and step 2 consists of a totally laparoscopic right trisectionectomy.[50,51] In addition, the first complete robotic ALPPS has been reported in Spain.[52] The findings of these studies indicate that ALPPS can be safely performed with minimal invasiveness. However, most of these studies were only case reports with a lower level of evidence, and advanced laparoscopic skills are required to perform the procedure. Thus, laparoscopic ALPPS cannot be recommended at the present time.

3.5. Left ALPPS, rescue ALPPS, and right ALPPS

In 2013, Gauzolino et al[53] described 3 modified forms of the original ALPPS procedure. Four patients were enrolled in their study: 1 underwent the original ALPPS procedure, 1 underwent left ALPPS, 1 underwent rescue ALPPS, and 1 underwent right ALPSS.

These 3 modified ALPPS were introduced in this article.[53] The left ALPPS includes the left PVL and ISS of the liver parenchyma along the main portal fissure. The rescue ALPPS means using the original ALPPS for the patients after PVE failed to result in satisfactory liver hypertrophy. In the right ALPPS, the postero-lateral branch of the right portal vein is ligated, and the ISS line is along the right portal fissure.

All 4 surgeries were successful and there were no postoperative mortalities, with only 1 patient (who underwent left ALPPS) experiencing a grade III complication. However, the original ALPPS procedure resulted in the greatest hypertrophy of the FLR. Over the 2 years that followed, several case reports verified the feasibility of these 3 modified forms.[54–56] Like the original ALPPS procedure, these modified forms allow surgical resection of hepatic lesions that were initially considered unresectable. However, the effectiveness and safety of these modified forms cannot be evaluated due to a lack of convincing and specific data.

3.6. ALTPS

Robles et al[25] in Spain described a new modified form of the ALPPS procedure which they termed associating liver tourniquet and portal ligation for staged hepatectomy (ALTPS) (Fig. 1B). Instead of ISS of the liver parenchyma, a tourniquet was placed on the umbilical ligament if a staged right trisectionectomy was planned, and a tourniquet was placed on Cantlie's line if a right hepatectomy was performed during the first surgery. The advantages of this new approach are the reduced operating time

for stage 1 because of the small amount of surgery performed and the ease with which ischemic parenchyma can be cut during stage 2. Moreover, the first stage leads to less blood loss and segment IV is not separated from the hilar bifurcation, thereby avoiding ischaemic necrosis of segment IV. Patients were discharged early after the first stage of ALTPS and there were no deaths after this stage, unlike in ALPPS.

3.7. Anterior approach in ALPPS

An anterior approach, that is, parenchymal transection without prior mobilization of the right lobe or visualization of the vena cava, is usually used for large right hemi-liver hepatomas. A group of surgeons in Hong Kong initially reported the use of an anterior approach in ALPPS in 2 patients.[57] Later, comments from Ardiles et al[58] revealed that 37% patients in the International ALPPS Registry underwent transection via an anterior approach during the first stage of ALPPS.

3.8. Hybrid ALPPS

Li et al[59] described a new approach to ALPPS in a letter to the *Ann Surg*. After reading a comment that ALPPS was supposedly an "all-touch" technique that would reduce the oncological effectiveness of the treatment of liver malignancies,[20] Li et al developed a nontouch technique to treat tumor infiltration of the right portal vein or biliary bifurcation as part of ALPPS (Fig. 1C). This modified approach was termed "hybrid ALPPS" (parenchymal transection in the first stage and portal vein embolization 1 day later). Hybrid ALPPS consists of 3 steps: surgical exploration and in situ splitting of the liver via an "anterior approach," right PVE via interventional radiology, and complete 2-stage hepatectomy. This Hybrid ALPPS could improve the oncological efficiency with "nontouch" technique which has been proven by previous study.[60] Especially, this modified ALPPS could be beneficial for patients with tumor infiltration of the right portal vein. However, the disadvantage of hybrid ALPPS is that the stage II surgery takes longer and requires the transfusion of more red blood cells due to the complexity of the surgery itself. Further studies are needed to evaluate this modified form of ALPPS in the future.

3.9. Partial ALPPS

In 2015, Petrowsky et al[61] described their experience with a modified form of ALPPS that they termed partial ALPPS (p-ALPPS) (Fig. 1D). Petrowsky et al performed a partial partition (50%–80%) rather than a full liver partition. In the stage 1, the initial goal was to transect at least 50% of liver parenchyma alone the transection line. They tried to preserve middle hepatic vein during stage 1, thus the location of the hepatic veins or tumor determined the different degrees of partial transection ranging from 50% to 80%. Data indicated that p-ALPPS is associated not only with zero mortality but also with a more favorable postoperative complication profile, especially after stage 1 surgery.[61] Later, objective boundaries for categorization of the dissection were provided: partial partition is defined as dissection to the level of the middle hepatic vein, whereas total partition is dissection to the vena cava.

In summary, some modified forms of ALPPS have reduced the mortality and morbidity of the original ALPPS procedure, but they cannot be recommended at the current time due to insufficient data.

4. Advantages and disadvantages of ALPPS

4.1. Advantage 1: rapid hypertrophy

By far, the biggest advantage of ALPPS is that it induces hypertrophy/growth of the FLR in a short period of time. ALPPS allows surgical resection of hepatic lesions that were initially considered unresectable. According to the literature, ALPPS results in a 47% to 93% increase in the FLR within 7 to 14 days (Table 1), which is an impressive outcome since TSH requires a median of 99 days (range: 32–210 days) to induce sufficient hypertrophy before the second surgery.[62]

The reason for this rapid hypertrophy is often discussed clinically. Although the key factors that initiate liver regeneration remain unclear, the physiological triggers for liver regeneration include 2 major proposals[63]: after partial hepatectomy, a stress signal is generated due to the increase of energy demand per unit liver volume; the altered hemodynamic factors. Although there is a definite correlation between blood flow and liver regeneration, the specific role of blood flow in liver regeneration remains unclear.[64] In addition, cytokines and growth factors are also essential components that are directly involved in liver regeneration. A recent experiment in mice by Schlegel et al[65] revealed that injury to other organs or ALPPS-plasma injection combined with PVL could induce liver hypertrophy similar to that induced by ALPPS. Schlegel et al concluded that the systemic release of circulating proliferating factors related to parenchymal transection is crucial to rapid and efficient liver growth.

Thus, a hypothesis can be put forth: during the first stage of ALPPS surgery, ISS of the liver parenchyma induces an energy demand and PVL alters hemodynamic factors. These phenomena accord with both of the theories mentioned earlier. If ALPPS triggers greater liver regeneration, this might explain why ALPPS induces hypertrophy to a greater extent and at a faster pace than PVE or PVL. However, a study has found PVE induces satisfactory hypertrophy in 4 weeks if extended to segment 4 (PVE+S4).[66] This is presumably because PVE+S4 stimulates the same levels of circulating proliferating factors as ALPPS does. Shear stress on endothelial cells is a powerful impetus for liver regeneration, regulation of liver volume, liver growth, and atrophy of the liver.[67] TSH only involves local resection during the first stage, resulting in less shear stress than ISS of the liver parenchyma in ALPPS. This could be the potential cause of more insufficient liver regeneration after TSH.

Basic studies of liver regeneration, and particularly those involving animal models, are urgently needed to determine the reason for the rapid hypertrophy of the FLR observed in ALPPS.

4.2. Advantage 2: feasibility and R0 resection

ALPPS appears to be a highly feasible method of treating primarily nonresectable liver tumors. According to the current review, stage 2 surgery was completed at a rate close to 100% (95%–100%), and a meta-analysis by Schadde et al[68] reported that ALPPS had a feasibility of 97%. This is an obvious advantage of ALPPS, since TSH only has a feasibility of 77%.[69] ALPPS involves a short interval between the first and second stages of surgery, so the progression of disease is quite rare. Moreover, hypertrophy of the FLR is sufficient to allow the second surgery in most cases. These 2 factors contribute to the high feasibility of ALPPS. However, there is concern that previous studies of ALPPS have underreported the rate of incomplete ALPPS procedures since ALPPS has been performed at many institutions without sufficient evaluation of its technical

and oncologic safety.[70] An R0 resection is the ultimate goal of ALPPS to treat an aggressive tumor of the liver, and all of the reviewed studies reported that an R0 resection was achieved at a rate varying from 83% to 100%, with the exception of 1 study where an R0 resection was achieved at a rate of 0%.[36] Because it allows achievement of an R0 resection, ALPPS has expanded the scope of curative resection. Indeed, monosegmental ALPPS has been reported.[71] Schadde et al[55] studied 12 patients who underwent monosegment ALPPS, and an R0 status was achieved in 83.3% (10/12). The 12 patients were all diagnosed with colorectal liver metastases (CRLM) and the liver remnant consisted of only 1 segment ± S1. The advantages of ALPPS in terms of feasibility and achieving an R0 resection indicate that this technique may be a way to cure patients with extensive CRLM.

4.3. Disadvantage 1: high mortality and morbidity

The aspect of ALPPS that is most often discussed is its high mortality and morbidity. When Schnitzbauer et al[19] initially described ALPPS, its morbidity rate of 68% and in-hospital mortality rate of 12% were the main aspects emphasized by surgeons who argued against the approach. However, ALPPS was not abandoned and its disadvantages led to the refinement of the technique. Thus, the current work has systematically reviewed the evolution of ALPPS. In addition to the studies cited thus far, Hernandez-Alejandro et al[33] reported that ALPPS had an overall rate of complications of 36% and a 90-day mortality rate of 0%. Hernandez-Alejandro et al minimized dissection of the hepatoduodenal ligament to preserve the arterial supply to segment 4 and the bile duct, and they also evaluated tumor biology in accordance with the response to preoperative chemotherapy while recruiting patients. These modifications greatly reduced the mortality and morbidity of ALPPS. Chan et al[39] used an anterior approach and they noted that only 1 (7.7%) of 13 patients had major complications (Dindo grade ≥ IIIB). Greater experience with ALPPS has apparently led to better selection of patients and establishment of a standard procedure.

4.4. Disadvantage 2: early tumor recurrence

Every coin has 2 sides. Despite its advantages, ALPPS may promote tumor growth. A recent study by Oldhafer et al[28] found that 6 of 7 patients had tumor recurrence with a median time of 8 months after ALPPS, and Oldhafer et al found that ALPPS had the same potential for tumor progression as PVE. A previous study noted increased proliferative activity in CRLM (a Ki-67 labeling index) after PVE of the embolized and nonembolized lobe.[72] Later studies by Hoekstra et al and Hayashi et al both noted increased tumor growth rates after PVE.[73,74] However, Shindoh et al reported that patients with CRLM who were properly selected based on the oncological activity of the tumor (no significant progression) to undergo curative resection after PVE had overall and disease-free survival rates equivalent to those of patients who did not undergo PVE.[75] The similarity in survival rates might be due to curative resection, which precluded the effective stimulation of tumor micrometastases. Although there is considerable evidence that PVE is associated with a greater recurrence of disease, a definitive conclusion has yet to be reached. Additional evidence regarding ALPPS was presented by Fukami et al,[76] who performed a biopsy of the same segment liver metastases immediately after the first and second laparotomy. The Ki-67 labeling index for tumor cells was 60% during the first surgery but increased to 80% during the second surgery. The maximum standardized uptake value, a marker of tumor glucose metabolism reflecting tumor aggressiveness that is detected with PET/CT, increased as well. Unfortunately, this evidence is weak because it comes from a small series. All of the original studies of ALPPS that reported tumor recurrence were reviewed. Early recurrence occurred but the data are not satisfactory since the rate of recurrence varied from 5% to 86% due to different follow-up times. The mechanism by which ALPSS stimulates tumor growth is still unclear, and different tumors have different characteristics. Better designed studies of a single type of tumor need to be conducted to determine if there is any relationship between ALPSS and early tumor recurrence.

5. Controversy

5.1. Posthepatectomy liver failure

Although ALPPS has received a favorable reaction from surgeons worldwide, its safety is still debated. De Santibanes et al[77] underlined the fact that 77% of deaths after ALPPS were due to posthepatectomy liver failure. This finding highlights the fact that rapid hypertrophy may not provide sufficient liver function to avoid PLF. In fact, Sotiropoulos and Kouraklis[78] commented on the restoration of liver function when ALPPS was initially reported. They mentioned an established finding, a tremendous short-term increase in volume within 10 days in healthy liver donors after right hepatectomy, but they also noted that the galactose elimination capacity decreased more than 40%, beginning at 10 days and persisting for up to 3 months. Galactose elimination capacity is a better indicator of liver function than liver biochemistry profiles and bilirubin levels. Thus, Nadalin et al[79] suggested that restored hepatic function cannot be based solely on normal liver biochemistry profiles and liver volume growth. Recently, Tanaka et al used 99mTc-GSA SPECT/CT to calculate the functional liver volume, and they found that patients undergoing ALPPS tended to have a smaller functional volume of the FLR 1 week after the first procedure (52.1%) than patients undergoing TSH did 3 weeks after the first procedure (59.2%). These studies suggest that allowing an adequate time for restoration of liver function is crucial to the FLR despite a sufficient increase in its volume. Therefore, optimal timing for the second stage of ALPPS should be determined. Fortunately, a team of surgeons from the University of Sao Paolo, Brazil, is doing just that using the ALPPS registry. Another key suggestion is the importance of estimating postoperative liver function. However, the basic method of estimation is still based on the remaining liver volume,[80] although indocyanine green clearance testing and 99mTc-GSA SPECT/CT are commonly used.[81,82] Many factors can influence the outcome of that testing, so deciding the best way to precisely estimate liver function is difficult. Thus, various tests need to be used in combination and function needs to be evaluated based on objective data.

5.2. Major complications

Major complications are another factor that usually causes death after ALPPS. The 2 main types of complications are sepsis and a bile leak. Early in the history of ALPSS, Andriani et al advocated resection of an ischemic segment 4 in the first stage to avoid septic complications related to its eventual necrosis.[21] In contrast, Alvarez et al noted no abscesses in segment 4 in their study of antibodies in the interval between stages.[37] Alvarez et al

contended that resection of segment 4 was unnecessary in ALPPS and they advised against this approach since the patient would undergo surgery again only a week later. To reduce the incidence of segment 4 necrosis, some surgeons have pondered whether the middle hepatic vein should be ligated as a venous outflow of segment 4. The First International Consensus Meeting on ALPPS recommended preserving this vein during splitting of the liver.[83] Most of the reviewed literature described a procedure to avoid segment 4 necrosis. In addition, some of the new forms of ALPPS, such as ALTPS and partial ALPPS, are similar in that they preserve segment 4. Ultimately, this position is supported only by clinical data since related basic experiments have yet to be performed in animals. A bile leak is reported in up to 20% of patients (ordinary hepatectomy <5%), and this is also associated with the sepsis caused by liver parenchymal necrosis.[36,84] Intraoperative cholangiography, routine use of T-tube drainage, and other approaches were also discussed at the first international meeting on ALPPS.[83] The incidence of bile leakage will presumably decrease as ALPPS is modified and refined.

6. Discussion

6.1. ALPPS versus other techniques

ALPPS casts doubt as to which tumors are unresectable and it also casts doubt as to whether other techniques are better. ALPPS is mainly compared to other techniques in 2 ways: ALPPS versus PVE in patients with a tumor-free FLR and ALPPS versus TSH in patients with a tumor involving the FLR.

6.2. Tumor-free FLR

Patients may have a small FLR but they may be fortunate in having an FLR free of tumors. The conventional approach is to use PVE to induce adequate contralateral liver hypertrophy to convert most patients to hepatectomy candidates. Previous studies have found that PVE increases the FLR between 7% and 27% (average: 12%) of total liver volume or between 20% and 46% beyond the pre-PVE FLR volume within 2 to 8 weeks.[85,86] ALPPS surpasses this approach because of its advantages of rapid hypertrophy and a short interval between surgeries. However, Madoff et al[87] used embolic microspheres and coils in percutaneous ipsilateral PVE extended to segment 4 to achieve a hypertrophy rate of up to 69%. Similarly, PVE has resulted in the same level of hypertrophy as ALPPS at the University of Tokyo.[88] PVE algorithms are still improving, so more facilities may achieve this level of hypertrophy in the future. Although PVE involves a long waiting time, PVE only requires 1 surgery and involves less trauma, making it superior to ALPPS. Moreover, Madoff et al found value in the waiting period, from an oncological perspective, since any existing infections can be cleared, the patient's performance status prior to major hepatectomy can be improved, and the patient can be reassessed for disease progression. A seasoned surgical team that performed ALPPS had the same viewpoint, contending that ALPPS will never replace PVE for patients with a tumor-free FLR.[77] However, ALPPS can be considered a salvage procedure. Tschuor et al performed ALPPS on 3 patients who underwent PVE/PVL with an insufficient increase in volume and they achieved satisfactory outcomes.[89]

6.3. Tumors involving the FLR

According to current guidelines on HCC and cholangiocarcinoma, tumors involving the FLR are generally considered to be unresectable if the patient needs local-regional therapy, chemotherapy, or supportive care.[90] However, a recent expert consensus statement and an original study of CRLM recommended that experienced centers perform TSH in cases of more advanced disease (tumors in the FLR).[91,92]

In patients with a tumor involving the FLR, the first surgery should remove that tumor, regardless of whether TSH or ALPPS is used. The differences between these 2 approaches are: TSH involves intraoperative PLV or postoperative/intraoperative PVE; ALPPS involves intraoperative PLV and in situ splitting of the liver. Few studies thus far have compared ALPPS and TSH.[31,34,36] In a study by Schadde et al, a complete resection was achieved with ALPPS in 83% of patients while a complete resection was achieved with TSH in 66% of patients. However, ALPPS had a 90-day mortality rate of 15% while TSH had a 90-day mortality rate of 6%. Schadde et al contended that ALPPS offered a better chance of complete resection at the cost of a higher mortality rate with no significant difference in recurrence at 1 year (ALPPS:TSH=54%:52%). In 2015, Ratti et al[34] compared ALPPS and TSH exclusively for treatment of CRLM. To adjust for the different covariate distributions in the 2 groups, Ratti et al scrupulously matched patients in the TSH group based on propensity scores. They found that ALPPS did not offer a significant advantage in terms of resectability. They also found that the overall rate of complications and the rate of major complications were significantly higher in the ALPPS group after stage 2 (Clavien grade ≥IIIA: 41.7 vs 17.6% in the TSH group). Tanaka et al[36] described some meaningful outcomes of ALPPS. They found that patients who underwent ALPPS had resected liver tumors with a lower level of Ki67 expression during the second hepatectomy than did patients who underwent TSH, suggesting an oncologic benefit of ALPPS since the short interval between the 2 surgeries helps to avoid the risk of tumor progression. However, patients who underwent ALPPS also had a higher mortality rate. All 3 of these studies verified that ALPPS has an advantage in terms of the extent of FLR hypertrophy. A meta-analysis verified that TSH was associated with low morbidity and mortality rates.[93] Unfortunately, few studies have compared modified forms of ALPPS, such as ALTPS, p-ALTPS, and hybrid ALPPS, to TSH, and few have compared these modified forms of ALPPS among themselves. Therefore, there is no evidence with which to judge which form of ALPPS is better. ALPPS is still evolving. According to a report at a conference in China, surgeons at the University of Tokyo have attempted to modify hybrid ALPPS by performing a partial resection instead of a full resection and by performing PVE during the first surgery. This modified technique has been performed in 3 patients, with satisfactory outcomes. Studies that compare TSH and modified forms of ALPPS may help to determine the most suitable form of ALPPS. More carefully controlled studies and an international multicenter randomized controlled trial conducted over the next 2 years may provide persuasive data.

6.4. The limitations of ALPPS

ALPPS has many limitations. ALPPS must be undertaken by experienced hepatobiliary surgeons in a high-volume hospital, and well-organized cooperation among radiologists and oncologists is required for patient selection.[94] A standard ALPPS procedure has yet to be established and its effectiveness is still debated, so ALPPS is not recommended for secondary hospitals. PVE clearly has many advantages, especially in terms of lower morbidity and mortality. Although the extent of liver

hypertrophy depends on the expertise of the surgeon, PVE is a better choice since it is easier to perform than ALPPS.[66] Hepatobiliary surgeons who have less experience could consider a modified form of ALPPS for appropriate patients because it has lower mortality and morbidity. Moreover, ALPPS should only be considered under several conditions, including bilobar lesions (a tumor involving the FLR), failure of FLR growth after PVE or PVL, and an R0 resection is feasible after ALPPS.

6.5. Indications and long-term oncologic outcomes

The highest level of evidence regarding ALPPS comes from analyses of cases in the ALPPS Registry. According to a meta-analysis,[68] the Registry includes 202 patients classified as level 2c. Up to 70% of those patients had CRLM. Resection has been increasingly accepted as standard treatment for CRLM. This is a consequence of the improved safety of liver resection and the mounting evidence in favor of an associated survival benefit.[95] Pulitanò et al[96] reported data from a 10-year follow-up indicating a curative effect after liver resection. In addition, patients with CRLM usually have normal liver function, unlike patients with HCC or ICC and hepatitis or cholangitis. Thus, ALPPS could reasonably offer a better rate of resectability in patients with CRLM. Schadde et al[68] noted that patients younger than 60 years of age who underwent ALPPS to treat CRLM had a 90-day mortality rate similar to that of patients who underwent TSH. In fact, many other liver diseases besides CRLM may require ALPPS,[97–99] but ALPPS has been reported to have an acceptable mortality and morbidity only when used to treat HCC, and its long-term results are highly limited.[39,100] HCC is still the most common liver tumor, and the death rate in Asia remains high due to delayed diagnosis or a lack of effective treatment besides liver resection.[101–104] Thus, further studies on ALPPS to treat HCC are warranted. Theoretically, ALPPS is highly suitable for treatment of hilar cholangiocarcinoma. Donati et al[105] summarized the reasons for this: pre-PVE that predetermines the side of the liver to be resected can be avoided, hepaticojejunostomy is performed during the first step to drain the cholestatic biliary tree, and the impact of small-for-size syndrome is reduced and the surgeon can check the liver remnant at the site of the hepaticojejunostomy and control a possible bile leak. However, indications for treatment of Klatskin's tumor are debated since the procedure is technically demanding and it has a high mortality. Only long-term oncological outcomes can ultimately indicate the usefulness of ALPPS. Lang et al[38] first assessed the long-term results of this aggressive 2-stage strategy for liver resection. They noted a median overall survival (OS) of 42 months and a median disease-free survival (DFS) of 14.6 months and they calculated the 3-year OS to be 56.4% (for CRLM) and 65.2% (for non-CRLM) when including postoperative mortality. Lang et al contended that the observed 3-year survival was similar to that obtained with other aggressive surgical approaches to treat CRLM and better than that achieved with chemotherapy alone. Well-designed studies of ALPPS need to be conducted. That said, the 5-year survival for ALPPS will be determined over the next 2 years. That period should provide a body of reliable data that will help to determine the indications for ALPPS and to select suitable patients.

6.6. Limitations of this systematic review

The first limitation of this review is the publication bias found in the 16 articles that were reviewed, and this bias might have affected the reported results. The second limitation is that the 12 reviewed studies had a small sample. The third limitation is that the reviewed studies represented a low level of evidence, and no RCTs were reviewed. Since the reviewed studies presented insufficient or varied data, a meta-analysis was not performed.

7. Conclusions

In the history of liver resection, ALPPS is like a newborn baby. It needs sufficient time to grow and mature. Although ALPPS has been reported as a novel approach with a high morbidity and mortality, this technique offers the chance to cure liver malignancies that could not be resected with other techniques. Three years have passed since ALPPS debuted, and ALPPS has evolved into several modified forms. Some of these modified forms of ALPPS have reduced its mortality and morbidity, but they cannot be recommended at the current time due to insufficient data. The advantages of ALPPS are rapid hypertrophy of the FLR, feasibility, and a high rate of R0 resection while the disadvantages of ALPPS are worse major complications, more deaths, and early tumor recurrence. According to the literature, indications for ALPPS are still being debated, but ALPPS is associated with better outcomes in CRLM and patients $\leq$60 years of age. PVE remains the treatment of choice for patients with no tumor involving the FLR, and ALPPS could be used as a salvage procedure when PVE fails. ALPPS and TSH require more persuasive evidence to determine which is better for patients with a tumor involving the FLR. Studies will be published in the next 2 years, and studies of the 5-year survival rate of ALPPS could ultimately help to determine the usefulness of ALPPS. Indications and patient selection for the procedure need to be determined.

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