

Role of associating liver partition and portal vein ligation in staged hepatectomy (ALPPS)—strategy for colorectal liver metastases

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Abstract: Colorectal carcinoma (CRC) is the third leading cause of cancer-related death in the United States. The liver is the most frequent site of metastasis and a key determinant of survival in patients with isolated colorectal liver metastasis (CRLM). Surgical resection remains the only hope for prolonged survival in patients with CRLM. However, most patients are deemed to be unresectable at presentation due to a small future liver remnant (FLR) and fear of post-hepatectomy liver failure. Procedures such as portal vein ligation or embolization (PVL/PVE) followed by hepatectomy have been established as standard methods to increase FLR volume, but have limitations dependent upon extent of disease and patient's ability to grow the liver remnant. Recently, associating liver partition and portal vein ligation in staged hepatectomy (ALPPS) has been introduced as a technique to induce liver hypertrophy over a shorter time period. Being a complex two-stage surgical procedure, initial reports of higher ALPPS-associated complications and mortality limited its worldwide adoption by hepatobiliary surgeons. However, recent studies have showed ALPPS superiority over conventional procedures in terms of feasibility and inducing liver hypertrophy, with comparable morbidity and mortality. We herein review the role of ALPPS in management of patients with CRLM.

Keywords: Associating liver partition and portal vein ligation in staged hepatectomy (ALPPS); colorectal; liver; outcomes

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Introduction

Colorectal carcinoma (CRC) is the third leading cause of cancer-related death in the United States (1). Almost 30% to 50% of patients with CRC develop liver metastases at sometime during the course of their disease (2,3). The extent of liver disease is a key determinant of survival in patients with isolated colorectal liver metastasis (CRLM). Although surgical resection remains the cornerstone of potentially curative therapy for patients with CRLM, few

patients (20–30%) are amenable to surgical resection at the time of presentation either due to tumor burden or non-resectable extrahepatic metastases (4). Maintaining adequate future liver remnant (FLR) volume to avoid post-hepatectomy liver failure (PHLF), while achieving R0 resection is the main technical challenge especially in patients with bilobar CRLM.

The potential of hepatocytes to proliferate with hemodynamic changes, particularly an increase in portal

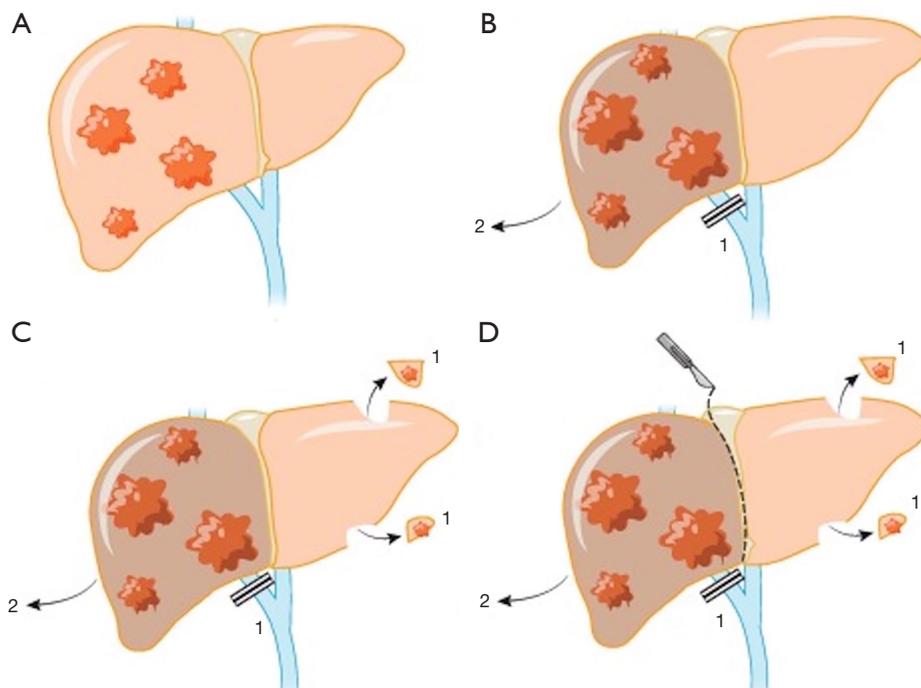


Figure 1 Visualization of pre- or peri-operative interventions and their effect on liver remnant volume. (A) Malignant liver disease; (B) embolization/ligation of the right portal branch, [1] resulting in atrophy of the right hemi-liver and compensatory growth of the left hemi-liver, which can be removed when appropriate hypertrophy has been achieved [2]; (C) removal of tumours from the left hemi-liver and occlusion of the right portal branch [1]. After 4–6 weeks, the volume of the left hemi-liver is increased and the right hemi-liver can be removed [2]; (D) removal of tumours from the left hemi-liver, in situ splitting of the hemi-livers, and simultaneous ligation of the right portal vein branch [1]. After 1-week, augmented hypertrophy of the left hemi-liver permits removal of the right hemi-liver [2].

venous flow, has led to development of a number of procedures aimed at increasing the volume and function of the FLR (5,6). Techniques such as portal vein embolization/ligation (PVE/PVL) followed by two-stage hepatectomy (TSH) have been established as standard procedures in management of patients with extensive metastatic liver disease. In 2007, Schlitt innovated a novel two-stage liver resection technique with the capability to rapidly enhance FLR volume before completion of surgical resection (7). Subsequently, Schnitzbauer *et al.* published the first clinical series on this novel technique in 2012 (8). Ultimately, the technique was named “associating liver partition and portal vein ligation for staged hepatectomy” (ALPPS) by de Santibañes *et al.* (7). We herein, reviewed the current role of ALPPS in the management of patients with CRLM.

Original surgical technique and subsequent modifications

ALPPS is a two-step procedure (Figure 1). In right lobe

dominant disease, in the first step, the liver is completely mobilized and the right portal vein branch is ligated. Subsequently, the liver parenchyma is transected along the falciform ligament. Wedge resection of any metastatic lesions in the FLR (segments I/II/III) is performed in the first step as well. The right liver lobe and segment IV are then typically placed in a plastic bag to avoid post-operative adhesions during the waiting period until the next operation, and the abdomen is closed. After an interval of 7–14 days, the growth of the FLR is assessed by CT volumetry. If the volume gain seems sufficient, the patient undergoes the second step, usually involving a right tri-sectionectomy. The biliary tract reconstruction, if needed, is performed with a Roux-en-Y hepaticojejunostomy (8). In patients with synchronous CRLM, the primary tumor is often resected during first-stage of ALPPS (9).

Various modifications of ALPPS have been reported in the literature, as more hepatobiliary centers started to adopt the procedure. In associating liver tourniquet and portal vein ligation for staged hepatectomy (ALTPS) introduced

Table 1 Summary of studies reported outcomes of ALPPS in CRLM patients

| Author/year | Indication | No. of (CRLM) cases | FLR vol. increase, % | Median interval, (days) | Morbidity | 90-day mortality, % | Median follow-up | Recurrence | Survival |
|---------------------------------------|----------------|---------------------|----------------------|-------------------------|-----------|---------------------|------------------|--------------|------------------------------|
| Schadde et al. (29), 2014 | CRLM+ non-CRLM | 141 | 80 | 7 [6–13] | 36% | 8 | –* | NR | 76% (1 year) 62% (2-year) |
| Oldhafer et al. (30), 2014 | CRLM | 7 | 65 | 13 [10–40] | 6 of 7 | 0 | 15 [8–25] months | 85% (6 of 7) | NR |
| Hernandez-Alejandro et al. (13), 2015 | CRLM | 14 | 93 | 8 [7–10] | 36% | 0 | 9.4 months | 14% | 100% (9 months) |
| Björnsson et al. (31), 2016 | CRLM | 23 | 64.30 | 5 [5–8] | 13.60% | 4.50 | 22.5 | 82% | 59% (2-year) |

ALPPS, associating liver partition and portal vein ligation in staged hepatectomy; CRLM, colorectal liver metastasis; NR, not report; FLR, future liver remnant.

by Robles *et al.*, instead of *in situ* splitting of the liver, a tourniquet was fixed along the future resection line to minimize the blood flow between the lobes (10). ALTPS was proposed to simplify the first step with reduced rate of adhesions and complications. The “anterior approach” was another modification that was suggested to minimize the peri-hepatic inflammation following the first step and hypothetically reduce the chance of hematologic spread of the malignancy (11). In the “anterior approach” complete liver mobilization was avoided and the hepatoduodenal ligament remained intact. Complete liver mobilization as well as dissection of all collateral flows ensures enough operative field exposure with enhanced rate of FLR hypertrophy, however, recent studies recommend minimal dissection of hepatoduodenal ligament to reduce the risk of both biliary leakage and segment 4 ischemia (12,13).

Several other technical modifications of ALPPS, according to the liver segment(s) that will comprise the FLR, have also been reported (14,15). In mono-segmental ALPPS, only one segment comprises the FLR (16,17). “Rescue ALPPS” refers to the ALPPS procedure performed in patients who did not achieve sufficient FLR following PVE to undergo the second step of TSH (18-21). ALPPS is considered as a last resort to induce liver hypertrophy in these patients. More recently, “laparoscopic first-stage ALPPS”, “totally laparoscopic ALPPS” and “robotic ALPPS” are minimally invasive approaches that have been reported to reduce the rate of postoperative adhesions and overall complications of the procedure (22-27).

Role of ALPPS in CRLM

Although ALPPS was initially reported in a patient with perihilar cholangiocarcinoma, shortly thereafter, CRLM patients constituted a considerable proportion of the candidates for this procedure (7,8,28) (Table 1).

In the first report of the international ALPPS registry of 202 patients, individuals with CRLM (n=141) had better prognosis compared to patients (n=61) with non-CRLM underlying diseases (29). The lower regenerative capacity of liver parenchyma and hence reduced regenerative capacity of the FLR in patients with primary liver malignancies, especially in the presence of fibrosis, might be the reason for the better outcomes of ALPPS among CRLM patients, who more often have normal liver function (29,32).

Recent advances in preoperative liver hypertrophy induction techniques and effective chemotherapy regimens, along with the advent of parenchymal-preserving liver

Table 2 Summary of studies reported outcomes of ALPPS *vs.* TSH

| Type of study | Ratti <i>et al.</i> , 2015 (42) | | | Adam <i>et al.</i> , 2016 (4) | | | Sandström <i>et al.</i> , 2018 (43) | | |
|--------------------------|---------------------------------|-----|-------|-------------------------------|-----|--------|-------------------------------------|-------|---------|
| | Retrospective, case-matched | | | Retrospective, case-matched | | | RCT | | |
| | ALPPS | TSH | P | ALPPS | TSH | P | ALPPS | TSH | P |
| No. of cases | 12 | 36 | | 17 | 41 | | 48 | 49 | |
| Increase in FLR vol. (%) | 47 | 41 | NS | NR | NR | | 68 | 36 | <0.0001 |
| Median interval (days) | 11 | 31 | 0.024 | 12 | 103 | <0.001 | 11 | 43 | <0.0001 |
| Morbidity (no.) | 10 | 13 | 0.011 | 7 | 16 | 0.99 | 19/44 | 12/28 | 0.99 |
| 90-day mortality | NR | NR | | 0 | 2 | 0.89 | 4 | 3 | 0.68 |
| Median follow-up | 12 | 37 | | 20 | 30 | | | | |
| Recurrence | NR | NR | | 8 | 17 | 0.28 | | | |
| Overall survival | 92 | 94 | NR | 42 | 77 | 0.006 | | | |

ALPPS, associating liver partition and portal vein ligation in staged hepatectomy; TSH, two-stage hepatectomy; NR, not report; RCT, randomized clinical trial.

surgery have expanded the limits of resectability in CRLM patients who were initially deemed to not be amenable to surgical resection because of insufficient FLR (3). Indeed, the ALPPS procedure has pushed the envelope even further and is a recommended choice of treatment in CRLM patients by the first ALPPS international expert meeting panel (33).

FLR hypertrophy

ALPPS may indeed be superior over PVE/PVL in inducing FLR hypertrophy in a shorter time interval. The liver hypertrophy in CRLM patients undergoing ALPPS has been reported to be as high as 110.3% in 7–14 days interval *vs.* 20–46% in 2–8 weeks following PVE (34,35). In a meta-analysis by Moris *et al.*, while preoperative FLR, the extent of FLR increase, and postoperative FLR were all similar between the two groups, the kinetic growth rate was faster with ALPPS *vs.* PVE (mean difference: 19.07 mL/day; 95% CI: 8.12–30.02, P=0.0006) (36). The technical differences between the two procedures and the associated underlying physiologic effects on hepatocytes have been proposed as potential causes of the differences in hypertrophy. Partitioning the liver in the first stage prevents collateral vessels flow between the two sides of the liver and maintains the shear stress of the portal flow on hepatocytes at its maximal level, a known physiologic factor contributing to liver regeneration (34,37). Moreover, traumatizing the liver parenchyma during the first step of ALPPS might augment the inflammatory mediators triggering hepatocytes' regeneration process (37). Of note,

some investigators have suggested that liver hypertrophy at 1 week does not necessarily guarantee functional capacity, and may reflect edema rather than true hypertrophy and new hepatocyte proliferation. As such, assessing the function of the FLR, with methods beyond routine biochemical liver profile, rather than just the size should be strongly considered (34,38).

Selective internal radiation therapy (SIRT), also known as radioembolization (RE) is a technique developed to deliver Yttrium-90 (Y-90)-labeled microspheres to hepatic tumors via the hepatic artery. In recent years, RE has evolved as an effective treatment in selected patients with liver malignancies not amenable to surgical resection. In addition to tumoricidal effects, the RE has been shown to induce contralateral liver lobe hypertrophy as well. The reported contralateral liver hypertrophy following the Y-90 RE ranges between 26–47% in a time interval of 44 days to 9 months (39,40). The slower rate of hypertrophy is the potential important limitation of considering Y-90 RE as a pre-surgical strategy. There is growing evidence in the literature that this approach could be considered for patients with large unresectable tumors, who may benefit from dual downsizing/control of the tumor as well as FLR hypertrophy (40,41).

Feasibility of completion hepatectomy

Another potential advantage of ALPPS over conventional TSH is higher feasibility for completion of both stages of the hepatectomy (*Table 2*).

Almost one-third of patients undergoing PVE/PVL followed by TSH for CRLM failed to complete the second stage resection with a feasibility of 65–75% (44). In contrast, a meta-analysis of patients with various underlying liver diseases who underwent ALPPS reported a completion hepatectomy feasibility of 97% (45). This proportion has increased to as high as 100% in studies including only CRLM patients (4,13,31). For example, in a study by Björnsson *et al.* the feasibility was 100% despite the fact that 43% of patients (n=10) underwent “rescue ALPPS” (31). Similarly, in a recent meta-analysis of 9 studies comparing ALPPS with TSH, the proportion of curative-intent resection, as well as the likelihood of proceeding to the second stage was higher in the ALPPS group compared with TSH [90.9% *vs.* 74.6%, respectively; risk ratio (RR) 1.21; 95% CI: 1.01–1.45, P=0.03] (36).

Tumor progression during time interval between two stages as well as insufficient FLR hypertrophy have been reported as two leading causes of patient drop out prior to completion hepatectomy in conventional TSH (44). While the shorter time prior to the second hepatectomy may increase overall feasibility, the shorter time interval between two stages in ALPPS might also hamper evaluation of the tumor biology and detection of micro-metastases that were not evident on initial imaging studies (46). This hypothesis has been supported by the relatively higher incidence of tumor recurrence and lower rate of disease-free survival (DFS) among patients undergoing ALPPS compared with conventional TSH (4,30).

Morbidity and mortality

PHLF, biliary leak and sepsis are serious complications of any liver resection. Current data comparing postoperative complications among CRLM patients undergoing ALPPS *vs.* conventional TSH has been contradictory. Ratti *et al.* compared outcomes of 12 ALPPS patients with 36 conventional TSH patients and reported that complications in the ALPPS group were higher than the TSH group (83.3% *vs.* 38.2%, respectively; P=0.011). There was one death reported in each group. No PHLF was observed in the ALPPS group, while two patients in the TSH group experienced liver failure. One-year overall survival (OS) and DFS were 92% and 67% in the ALPPS group *vs.* 94% and 80% in TSH group, respectively. In a different study by Adam *et al.* of 17 ALPPS and 41 conventional TSH patients, the incidence of major complications was no different between the two groups (41% *vs.* 39%, respectively;

P=0.999). The 2-year OS of 42% in the ALPPS group was, however, lower than in the TSH group (77%, P=0.006); in contrast, DFS was comparable (4,42). Olthof *et al.* reported that the 2-year OS of patients with CRLM who underwent ALPPS depended on the liver tumor burden and varied between 49% and 72% (47). Interestingly, the OS of a group of patients with extensive liver disease who underwent ALPPS was comparable with a matched group of patients with unresectable CRLM who were treated with palliative chemotherapy (24 *vs.* 17.6 months, P=0.088). In the Björnsson *et al.* study of 23 patients with CRLM, the 2-year OS was 59% and severe complications occurred in 13.6% of patients (31).

In the first international registry study, the 90-day postoperative mortality among all patients who underwent ALPPS with different underlying liver diseases was 9% (29). For patients with CRLM, the 2-year OS and DFS were 62% and 41%, respectively. Of note, CRLM patients younger than 60 years had a better survival than patients with other pathologies. In a study of fourteen patients with CRLM who underwent ALPPS, Hernandez-Alejandro *et al.* reported that OS was 100%, but median follow-up was only 9 months (13). Severe complications developed in only two patients. Moreover, only two patients experienced recurrence within 9 months. A separate analysis of the international ALPPS registry included 228 patients with CRLM, which comprised 72% of the study population. In this report, the 90-day mortality among CRLM patients who underwent ALPPS was 5% (48). The leading cause of mortality in patients with various underlying liver pathologies was “liver-related”. In turn, the authors suggested that the model of end-stage liver disease (MELD) score and the international study group for liver surgery (ISGLS) criteria could be utilized to discriminate between high and low risk patients. Developing liver failure following the first stage hepatectomy and MELD score of 10 or more prior to the second stage were independent predictors of 90-day mortality. The critical point to be considered in interpretation of any data comparing postoperative outcomes of these two procedures is that conventional TSH has typically been performed in younger CRLM patients, which are predictors of favorable outcome in ALPPS patients. However, current ALPPS data includes a substantial number of high-risk older patients with primary liver malignancies. The reported mortality rate of ALPPS for CRLM patients in general and for CRLM patients younger than 60 years of age were 8% and 5%, respectively, which are comparable to the reported mortality of TSH (49,50).

Stratification of patients for development of liver failure

following the first stage hepatectomy, achieving expertise in the learning curve, refinements in patient selection, modifications applied to the original ALPPS procedure to decrease liver traumatization, interval chemotherapy, shorter time off chemotherapy, and preservation of segment 4 are some of the suggested approaches to enhance ALPPS outcomes in CRLM patients. Clinical studies with larger number of cases are required to confirm and better evaluate these possible improvements to the ALPPS approach.

Deciding whether ALPPS may be best option for patients with CRLM

Recently, Sandström *et al.* published the first multicenter randomized controlled trial comparing ALPPS and conventional TSH in patients with advanced CRLM (43). Patients with CRLM and FLR <30% were randomly assigned to ALPPS (n=48 patients) and TSH (n=49 patients). The primary outcome of successful resection of all liver disease was higher in ALPPS *vs.* TSH group (92% *vs.* 57%, respectively; $P < 0.0001$). The incidence of major complications was the same in both groups (43%, $P = 0.99$). Five patients (11%) in the ALPPS group underwent reoperation due to intestinal obstruction, wound rupture, and bile leak, while only one patient (3%) required reoperation in the TSH group due to intestinal obstruction ($P = 0.25$). Notably, 13 patients (27%) in the TSH group dropped out before proceeding to the second stage hepatectomy. Twelve patients out of these 13 patients underwent rescue ALPPS, while the other one patient had tumor progression that prevented further surgery. After including these 12 “rescue” ALPPS cases in the TSH group, the resection rate in TSH group was 82% *vs.* 92% in the ALPPS group, although the difference was not statistically significant ($P < 0.1$). Ninety-day mortality in the ALPPS (9.1%) and TSH (10.7%) groups was comparable ($P = 0.64$). Despite the results on this one small-randomized study, ALPPS should generally not be considered as first line treatment for patients anticipated to achieve an adequate FLR with conventional PVE/PVL techniques. Rather, ALPPS should be reserved as an adjunct procedure for that subset of patients deemed to be not amenable to surgical resection with conventional procedures.

Conclusions

ALPPS has been reported to have a high feasibility and markedly induce FLR hypertrophy, which can broaden

the eligibility of patients who have extensive tumor disease for surgical resection. In selected patients with extensive CRLM, ALPPS has acceptable morbidity and mortality compared with TSH. While conventional approaches such as PVE/PVL and TSH will generally be applicable in most patients with extensive CRLM, ALPPS may have a role in a subset of patients to increase the number of patients eligible for surgical resection.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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