

## Current status of associating liver partition with portal vein ligation for staged hepatectomy: Comparison with two-stage hepatectomy and strategies for better outcomes

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### Abstract

Since its introduction in 2012, associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) has significantly expanded the pool of candidates for liver resection. It offers patients with insufficient liver function a chance of a cure. ALPPS is most controversial when its high morbidity and mortality is concerned. Operative mortality is usually a result of post-hepatectomy liver failure and can be minimized with careful patient selection. Elderly patients have limited reserve for tolerating the demanding operation. Patients with colorectal liver metastasis have normal liver and are ideal candidates. ALPPS for cholangiocarcinoma is technically challenging and associated with fair outcomes. Patients with hepatocellular carcinoma have chronic liver disease and limited parenchymal hypertrophy. However, in selected patients with limited hepatic fibrosis satisfactory outcomes have been produced. During the inter-stage period, serum bilirubin and creatinine level and presence of surgical complication predict mortality after stage II. Kinetic growth rate and hepatobiliary scintigraphy also guide the decision whether to postpone or omit stage II surgery. The outcomes of ALPPS have been improved by a combination of technical modifications. In patients with challenging anatomy, partial ALPPS potentially reduces morbidity, but remnant hypertrophy may compare unfavorably to a complete split. When compared to conventional two-stage hepatectomy with portal vein embolization or portal vein ligation, ALPPS offers a higher resection rate for colorectal liver metastasis without increased morbidity or mortality. While ALPPS has obvious theoretical oncological advantages over two-stage hepatectomy, the long-term outcomes are yet to be determined.

**Key words:** Associating liver partition with portal vein ligation for staged hepatectomy; Two-stage hepatectomy; Patient selection; Surgical outcomes

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**Core tip:** Associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) is associated with high morbidity and mortality. Operative mortality is usually a result of post-hepatectomy liver failure. Young patients with colorectal liver metastasis are ideal candidates. ALPPS for cholangiocarcinoma is associated with fair outcomes. In patients with challenging anatomy, partial ALPPS reduces morbidity, but remnant hypertrophy may compare unfavorably to a complete split. When compared to conventional two-stage hepatectomy with portal vein embolization or portal vein ligation, ALPPS has a higher resection rate. However, the long-term outcomes are yet to be determined.

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## INTRODUCTION

Functional reserve of future liver remnant (FLR) is the most important factor limiting surgical resection of liver tumors. In the last decade, extensive liver resection with a marginal FLR has been tackled with two-stage hepatectomy (TSH)<sup>[1]</sup>. Portal vein occlusion with surgical ligation or radiological embolization is performed in the first stage to induce hypertrophy of FLR. Redistribution of portal flow constitutes a stimulus to hypertrophy. Introduced in 2012, associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) encompasses parenchymal splitting and portal vein ligation in the first stage<sup>[2]</sup>. Complete redistribution of portal blood flow accelerates and enhances magnitude of FLR hypertrophy. Accelerated hepatic regeneration also minimizes disease progression during the inter-stage period and exclusion from surgery. ALPPS significantly expanded the pool of candidates for liver resection but was associated with significant operative morbidity and mortality<sup>[3]</sup>. Early results of this novel procedure have been more readily reported and may provide insights on how to improve the outcomes. The objective of this review is to summarize current available literature to compare the efficacy of ALPPS *vs* conventional TSH and to determine the strategies to make ALPPS a better surgery.

## ALPPS: BETTER THAN TWO-STAGE HEPATECTOMY?

The principle of oncological liver resection is complete tumor clearance while preserving adequate functional liver remnant. Inadequate FLR and extensive bilobar disease are common contraindications to curative resection. Before the era of ALPPS, TSH with portal vein embolization (PVE) or portal vein ligation (PVL) was validated to enlarge FLR prior to major hepatectomy. PVE boosted the FLR by 12%-62% over 3-8 wk<sup>[4-9]</sup>. In patients with diffuse bilobar disease, resection was achieved through a staged approach. In the first operation, tumors in the intended FLR were resected, *i.e.* clean-up resection and PVL is performed. The remnant was allowed to undergo hypertrophy while disease progression was controlled with systemic therapy before tumor clearance was completed in the second stage operation. ALPPS has been compared to TSH with PVE or PVL in terms of operative and oncological outcomes in recent publications.

### Operative outcomes

ALPPS consistently offered a more pronounced hypertrophy rate (50%-80% *vs* 10%-40%) over a shorter interval (7-11 d *vs* 20-103 d), enabled higher resection rate (80%-100% *vs* 60%-90%)<sup>[4-10]</sup> (Table 1). However, the inception of ALPPS was also met by criticism for the associated morbidity and mortality. In the initial series reported by Schnitzbauer *et al*<sup>[2]</sup>, operative mortality was 12%. The international registry reported a major morbidity (Clavien-Dindo IIIa or above) rate of 40% and an operative mortality rate of 9%<sup>[3]</sup>. From the captioned series a 20%-40% major complication rate (Clavien-

Dindo grade IIIa or above) was generally reported for both approaches<sup>[4-10]</sup>. Bile leak, intra-abdominal collection and pleural effusions were common complications encountered<sup>[9]</sup>. Pooled data from a meta-analysis did not reveal a statistically significant difference in overall morbidity. However, a comparison in terms of major morbidity had not been made<sup>[12]</sup>. Occurrence of post-hepatectomy liver failure (PHLF) (10% *vs* 14%, OR = 0.86) and 90-d mortality (9% *vs* 5%, OR = 1.44) were similar among patients operated with both approaches<sup>[12]</sup>.

Sandstrom *et al*<sup>[13]</sup> conducted a prospective randomized LIGRO trial to compare ALPPS and TSH in 100 patients with colorectal liver metastasis (CRLM) and FLR/estimated standard liver volume (ESLV) < 30%. The mean FLR/ESLV ratios were 22% and 21% in the ALPPS and TSH groups, respectively. Of the 48 patients in the ALPPS group, 44 (92%) attained satisfactory FLR/ESLV, *i.e.* 30% and completed stage II hepatectomy within 14 d. In contrast, thirteen (27%) patients in the TSH group (*n* = 49) never acquired sufficient remnant volume, and eight (16%) suffered disease progression preventing them from proceeding with second stage hepatectomy. It was noteworthy to highlight that twelve (24% of TSH arm) of them were successfully treated with rescue ALPPS. The prospective trial confirmed a higher resection rate (92% *vs* 57%, *P* < 0.001) for ALPPS with similar major morbidity (43% *vs* 43%, *P* = 0.99) and 90-d mortality (8% *vs* 6%, *P* = 0.68) with TSH.

### Oncological outcomes

CRLM is the most common indication for ALPPS. Theoretically accelerated remnant growth in ALPPS shortens the interval to definitive resection and minimizes dropout due to disease progression. Skepticism remains while a manipulated hemiliver with high tumor load is left *in vivo* within an immunosuppressed and stressed environment, and that rapid hypertrophy could trigger residual tumor progression<sup>[14,15]</sup>. In the setting of TSH for CRLM, tumor progression has been documented radiologically by accelerated tumor growth, and pathologically by increased mitotic rate and Ki67 index<sup>[16-19]</sup>. However, similar findings were not observed in ALPPS patients. Tanaka *et al*<sup>[8]</sup> compared Ki67 expression in both approaches showing significantly induced of Ki67 index in PVE but not ALPPS patients. Joechle *et al*<sup>[20]</sup> concluded that markers of tumor proliferation and angiogenesis were similar among patients undergoing ALPPS and standard liver resection.

Oldhafer *et al*<sup>[21]</sup> reported frequent early recurrence after ALPPS for CRLM. Over a median follow up of 7 mo, six out of seven patients (86%) developed recurrence. The median disease-free survival (DFS) was 7 mo (3-13 mo). However, the outcomes could have been accounted for by the relatively advanced disease status. The mean number of tumors was 7.6 (3-14), and the mean tumor diameter was 4.9 cm (1.7-11.3 cm). From the registry, the 1- and 2-year overall survival (OS) for CRLM were 76% and 62%, respectively<sup>[3]</sup>, comparable with a 67% 3-year OS reported for a large series of TSH<sup>[22]</sup>. While most case-control studies reported heterogeneous indications, comparison of CRLM outcomes was limited to two small retrospective series (Table 1). Ratti *et al*<sup>[6]</sup> compared 12 patients who underwent ALPPS with 36 TSH controls matched in terms of loco-regional staging and liver tumor status. With minimal dropout in the TSH arm (6%), 1-year overall (92% *vs* 94%) and DFS (67% *vs* 80%) were comparable. R0 resection rate was 100% among patients with completed resection procedures in both arms.

Adam *et al*<sup>[9]</sup> reported median OS was lower for the ALPPS arm at 2-year (42% *vs* 77%, *P* = 0.006) despite a higher completion rate (100% *vs* 63%, *P* < 0.001). This result compared unfavorably with registry data (2-year OS = 62%) and had to be interpreted with caution. R0 resection rates were low (17.6% *vs* 19.5%, *P* = 0.67) in both arms. Indeed, most patient in this series, irrespective of treatment arm, recurred early (1-year DFS 0% *vs* 10%, *P* = 0.21). An advanced preoperative disease status could be the culprit. Six (35%) and twelve (29%) patients had extrahepatic disease upon surgery in the ALPPS and TSH arms, respectively, and the median number of liver metastases were ten (compared to five reported in Ratti *et al*<sup>[6]</sup>). The inferior oncological outcomes could be the results of aggressive tumor biology rather than the choice of surgical approach.

In the more recent LIGRO trial, R0 resection rates were not different between ALPPS and TSH (77% *vs* 57%, *P* = 0.11), but survival data has yet to be available<sup>[13]</sup>. Long term oncological outcome of ALPPS is sparse due to its recent introduction. Whether ALPPS's conceptual advantages would translate to actual benefits over TSH remains unanswered.

**Table 1** Associating liver partition with portal vein ligation for staged hepatectomy vs two-stage hepatectomy, *n* (%)

<i>n</i>	Tumor	Preopera- -tive FLR/ESL- V in %	FLR increase in %	Interval in d	Comple- -te planned resection	Major morbidity, ≥		PHLF, ≥ B	HM	OS	DFS
						Stage I	Stage II				
Case control											
Schadde <i>et al</i> <sup>[1]</sup> , 2014	48/83	CRLM/H CC/CC	0.47/0.53 <sup>b</sup>	-	-	48 (100)/54 (64)	-	-	-	-	-
Shindoh <i>et al</i> <sup>[4]</sup> , 2013	25/144	CRLM/H CC/CC	-	74 (21-192) /62 (0- 379)	9 (5-28) /31 (12- 385)	-	10 (40)/34 (33)	-	3 (12) /6 (6)	-	-
Croome <i>et al</i> <sup>[5]</sup> , 2015	15/53	CRLM/H CC/CC	20 ± 4/31 ± 14	84 ± 8/36 ± 27	-	15 (100) /42 (79)	-	-	2 (13) /12 (23) <sup>c</sup>	0/2 (4)	-
Ratti <i>et al</i> <sup>[6]</sup> , 2015	12/36	CRLM	22/23	47/41	11/31	12 (100) /34 (94.4)	0/1 (2.8)	5 (42) /6 (18) <sup>d</sup>	0/2 (5.9)	1 (8.3) /1 (2.9)	1 yr: 92%/94% 1 yr: 67%/80%
Tanaka <i>et al</i> <sup>[9]</sup> , 2015	11/54	CRLM/N ET	34 ± 10/31 ± 10	52 (33- 94)/22 (34-68) <sup>e</sup>	-	11 (100)/48 (89)	1 (9)/4 (8)	3 (27)/8 (17)	5 (45)/5 (9)	1 (9)/1 (2)	-
Adam <i>et al</i> <sup>[9]</sup> , 2016	17/41	CRLM	24/30	50/33	12/103	17 (100)/26 (63.4)	4 (24)/7 (17)	4 (24)/10 (38)	0/1 (3.8)	0/2 (4.9)	2 yr: 42%/77% 1 yr: 0%/10%
Matsuo <i>et al</i> <sup>[11]</sup> , 2016	8/14	CRLM/C C	-	-	11 ± 2/52 ± 33	-	1(13)/4 (29)	2 (25)/8 (57)	0/0	-	-
Chia <i>et al</i> <sup>[7]</sup> , 2018	10/29	HCC/ CRLM	22 (12-29) /22 (15- 32)	48 (39- 97)/12 (4- 42)	7 (7-9)/20 (18-29)	8 (80)/12 (59)	3 (30) <sup>f</sup>	2 (25) <sup>g</sup> /3 (17.6) <sup>h</sup>	2 (25)/0 <sup>c</sup>	1 (3.4)/0	-
Meta-analysis											
Zhou <i>et al</i> <sup>[12]</sup> , 2017	201/518	-	-	WMD +40%	WMD - 27%	97%/73%	OR 2.4 <sup>i</sup>	OR 4.0 <sup>i</sup>	10%/14%	-	-
Randomized controlled trial											
Sandstro m <i>et al</i> <sup>[13]</sup> , 2018 <sup>j</sup>	48/49	CRLM	22.4 ± 4.3/21.2 ± 5.1	68 ± 38/36 ± 18	11 ± 11/43 ± 15	44 (92)/28 (57)	19 (43)/12 (43) <sup>k</sup>	4 (8.3)/3 (6.1)	4 (8.3)/3 (6.1)	-	-

<sup>a</sup>Among completed procedures.

<sup>b</sup>Future liver remnant/body weight.

<sup>c</sup>50-50 criteria.

<sup>d</sup>Bile leak (*n* = 1), intra-abdominal abscess (*n* = 3).

<sup>e</sup>Week 1.

<sup>f</sup>Pleural effusion (*n* = 2), wound dehiscence (*n* = 1).

<sup>g</sup>Pleural effusion (*n* = 1), post-hepatectomy liver failure (*n* = 1).

<sup>h</sup>Bowel ischemia (*n* = 1), acute renal failure (*n* = 1), pleural effusion (*n* = 1).

<sup>i</sup>All morbidity.

<sup>j</sup>Combined results of portal vein embolization (*n* = 27) and staged hepatectomy (*n* = 22) compared with associating liver partition with portal vein ligation for staged hepatectomy (*n* = 48).

<sup>k</sup>Clavien-Dindo IIIa or above. CC: Cholangiocarcinoma; CRLM: Colorectal liver metastasis; Cx: Complications; DFS: Disease-free survival; ESLV: Estimated standard liver volume; FLR: Future liver remnant; HCC: Hepatocellular carcinoma; HM: Hospital mortality; NET: Neuroendocrine tumor; OS: Overall survival; PHLF: Post-hepatectomy liver failure; WMD: Weighed mean difference.

## RISK FACTORS FOR MORBIDITY AND MORTALITY

The major morbidity associated with ALPPS were PHLF and bile leak. Understanding the risk factors allow better patient selection for better outcomes.

### PHLF

PHLF accounted for 75% of ALPPS related mortality<sup>[3,22]</sup>. Using the 50-50 criteria<sup>[23]</sup>, the international registry reported a 9% PHLF rate. Despite a rapid median volume gain of 80% before stage II, 80% of the patients with PHLF had an FLR of more than 30% of the total liver volume prior to stage II. Critics suggested that rapid remnant expansion in ALPPS was partly a result of tissue edema rather than pure hypertrophy<sup>[24]</sup>. There was also concern if the increase in volume had been paralleled by a corresponding increase in function<sup>[25,26]</sup>. The query was supported by the discrepancies between

volume gain and functional assessment using hepatobiliary scintigraphy. Inter-stage functional increment assessed by (99m)Tc-Mebrofenin scan only attained half the value of volume expansion<sup>[27]</sup>. This may in part explain the remarkable PHLF rate after ALPPS stage II despite satisfactory volume.

In an analysis of 320 patients in the registry to identify risk factors for 90-d mortality<sup>[22]</sup>, the single most important risk factor was patient age > 60 years (OR = 14.3,  $P = 0.001$ ). Inter-stage biochemical parameters were also predictive of mortality. Model of end-stage liver disease score > 10 prior to stage II (OR = 4.9,  $P = 0.006$ ) and liver failure defined by International Study Group of Liver Surgery (prolonged international normalized ratio and raised serum bilirubin) at day 5 after stage I (OR = 3.9,  $P = 0.011$ )<sup>[28]</sup> were independent risk factors for PHLF after ALPPS. These were simple, objective and reproducible laboratory parameters that allowed clinicians to assess the risk of proceeding to stage II operation.

Another study based on data collected from the registry generated a risk model for prediction of operative mortality after ALPPS (Table 2)<sup>[29]</sup>. Stage I poor risk indicators included advanced age (> 67, OR = 5.7) and biliary malignancy (OR = 3.8). Stage II predictors included cumulative stage I risk score (OR = 1.9), severe stage I complication (> IIIb, OR = 3.4) and serum level of bilirubin (OR 4.4) and creatinine (OR 5.4). Perhaps patient selection is most important before stage I. Advanced age was given a risk score of 3, while biliary tumor and non-CRLM/non-biliary tumor were given scores of 2 and 1, respectively. A total score of 0, 1, 2, 3, 4 and 5 were associated with operative mortality of 3%, 5%, 9%, 15%, 24% and 37%, respectively. The risk model provided an objective prediction of mortality. The message behind was straightforward: By avoiding elderly patients the total risk score was capped as 2, *i.e.* a mortality of 9%. Furthermore, this score provided guidance for a decision to postpone or omit stage II operation. The inclusion of serum bilirubin and creatinine level suggested postponing stage II until liver and renal function improved and was in concordance with the observation of higher mortality when stage II was proceeded with a high model for end-stage liver disease score (> 10, OR = 4.9,  $P = 0.006$ )<sup>[22]</sup>. Nonetheless, it was worthy to highlight that the addition of stage I cumulative score, *i.e.*, age, indication and stage I complications implied that presence of these poor risk factors despite normal liver and renal function still incurred stage II operative risk.

From experience in PVE, we learned that FLR growth rate was related to hepatic regenerative potential<sup>[30,31]</sup>. A kinetic growth rate of > 2%/wk was associated with fewer PHLF after hepatectomy. Its significance in ALPPS was investigated by Kambakamba *et al*<sup>[32]</sup> in a retrospective series of 38 procedures. It appeared to be a more reliable predictor of PHLF than FLR volume alone. Kinetic growth rate  $\geq 6\%/d$  and FLR > 30% at 1 wk after ALPPS stage I were associated with no PHLF. It compared closely to the median kinetic growth rate in the registry of 7%/d<sup>[3]</sup>. On the other hand, Serenari *et al*<sup>[33]</sup> deployed hepatobiliary scintigraphy with (99m) Tc-Mebrofenin scan for inter-stage remnant function assessment and developed a model termed 'The HIBA index' to predict PHLF. In their cohort of 20 patients, a cut off value of less than 15% predicted PHLF by a sensitivity of 100% and a specificity of 94%. These results indicated that hepatobiliary scintigraphy could be a useful adjunct to biochemical test and liver volumetry to assess remnant function. Patients with suboptimal remnant function could be allowed more time for further hypertrophy and safe resection.

### **Bile leak**

One of the most commonly reported surgical complications associated with ALPPS in the early days was bile leakage. According to the registry, bile leak occurred in 17% of ALPPS procedures<sup>[3]</sup>. The most common site of leakage occurred at the transection surface from the deportalized liver due to ischemia of segment IV when the portal vein was ligated, and the parenchymal split was between the left medial and lateral section parenchymal partition. The risk is particularly high for ALPPS performed for right trisectionectomy<sup>[34]</sup>. This was in particular an important issue in right trisectionectomy when the segment IV was instantly deprived of both portal and arterial perfusion that in turn resulted in necrosis followed by bile leakage and sepsis.

Cholangiocarcinoma is another risk factor for bile leak<sup>[35]</sup>. Hilar dissection is technically difficult due to tumor infiltration. Portal lymphadenectomy further deprived the transection plane of blood supply<sup>[36]</sup>. ALPPS associated morbidities were closely related to procedural complexity. Indeed from the registry independent risk factors for severe complications (Clavien-Dindo IIIb or above) were prolonged stage I operating time (more than 300 min) (OR = 4.42,  $P = 0.004$ ), blood transfusion (OR = 5.26,  $P = 0.001$ ) and non-CRLM (OR = 2.73,  $P = 0.049$ )<sup>[3]</sup>. ALPPS for hilar cholangiocarcinoma was not only associated with more bile leak but also more PHLF and operative mortality<sup>[35,37]</sup>.



**Table 2 Risk modelling proposed by Linecker *et al*<sup>[23]</sup>**

Risk modelling	Risk points	OR (95%CI)
Pre-stage I variables		
CRLM	0	1
Non-CRLM/non-biliary	1	1.925 (0.808-4.585)
Biliary	2	3.767 (1.800-7.822)
Age ≥ 67	3	5.668 (2.843-11.300)
Pre-stage II variables		
Pre-stage I score	0.66	1.925 (1.527-2.426)
Inter-stage complications ≥3b	1.2	3.350 (1.280-8.769)
Bilirubin	1.5	4.439 (1.699-11.600)
Creatinine	1.7	5.454 (1.606-18.520)

CI: Confidence interval; CRLM: Colorectal liver metastasis; OR: Odds ratio.

## STRATEGIES TO IMPROVE OUTCOMES

Many innovative surgeries faced unfavorable outcomes when they were first introduced. With accumulation of experience, improved outcomes were achieved with more cautious patient selection and more sophisticated technical refinements. A well-established international registry allowed information regarding ALPPS to be systematically collected<sup>[3]</sup>. With better understanding and insights into the procedure hepatobiliary surgeons could better select the suitable candidates and further refine their techniques to achieve more desirable outcomes.

### Patient selection

**Patient factor:** Elderly patients are poor candidates for ALPPS. From the international registry, patients older than 60 years of age had more severe complications (Clavien-Dindo IIIb or above) (OR = 3.76, *P* = 0.007)<sup>[3]</sup> and higher mortality (OR = 14.3, *P* = 0.001)<sup>[22]</sup>. Moreover, inferior OS were consistently observed for elderly patients with CRLM<sup>[3]</sup> and hepatocellular carcinoma (HCC)<sup>[38]</sup>. ALPPS is a physiologically challenging operation. Although a chronological cut-off may be impractical, it is rational to avoid ALPPS in patients with advanced physiological age. They have limited reserve to survive major complications, which are not uncommonly encountered. In these patients, TSH can be considered alternatively.

**FLR volume:** For major hepatectomy, an FLR to ESLV ratio of 25% is mandatory to ensure adequate postoperative liver function in patients with normal liver<sup>[39-41]</sup>. The requirement is 30% in patients with underlying liver disease *e.g.*, cirrhosis, cholestasis, *etc*<sup>[40]</sup>. When FLR deems insufficient, TSH with PVE or PVL is an established strategy, which induces 10%-30% FLR hypertrophy over 4-6 wk<sup>[42]</sup>. However, inadequate hypertrophy and disease progression prevent 10%-40% patients from proceeding stage II hepatectomy<sup>[4-6,11,43,44]</sup>.

ALPPS offers accelerated and pronounced hypertrophy. A 40%-80% hypertrophy is consistently observed over 7-10 d<sup>[4-6,11,43,44]</sup>. Conceptually, ALPPS would be most beneficial when FLR is extremely marginal or risk of inter-stage disease progression is high, *i.e.* aggressive and extensive tumor, for PVE/PVL would unlikely be effective. When ALPPS was compared head-to-head against PVE/PVL in the prospective LIGRO trial, the inclusion FLR/ESLV was defined as less than 30%<sup>[13]</sup>. A lower FLR/ESLV was generally accepted for ALPPS. Ratti *et al*<sup>[45]</sup> suggested performing ALPPS for patients with FLR less than 20% who were not expected to achieve sufficient remnant volume with conventional TSH. Consensus has not been reached on the ideal indicating FLR for ALPPS. Perhaps it would be rational to accept higher procedural risks when sufficient remnant growth is unlikely with conventional TSH. Reviewing current experience through the international registry, the median pre-stage I FLR was 21% (interquartile range: 17%-27%) of ESLV<sup>[3]</sup>. FLR hypertrophied by 80% over a 7-d interval producing an FLR to ESLV ratio of 40% (interquartile range: 31%-47%)<sup>[3]</sup>. ALPPS for extremely marginal ALPPS should be reserved for good risk patients in experienced centers, while increased operative morbidity and mortality should be expected. Patients with less marginal remnant volume can be considered for TSH.

**Disease factor - CRLM:** CRLM is the leading indication for ALPPS. To date, more

than 400 ALPPS have been performed for CRLM worldwide, including 220 right trisectionectomies and over 180 right hepatectomies<sup>[46]</sup>. Normal liver function and favorable tumor biology confers advantageous operative and oncological outcomes. Data from the registry concluded CRLM as an independent predictor of fewer severe complications (OR = 0.37,  $P = 0.049$ )<sup>[3]</sup>. Major morbidity (Clavien-Dindo 3a or above) occurred in 36% of CRLM patients, and the figure was further reduced to 29% when only patients younger than 60 years of age were selected<sup>[3]</sup>.

ALPPS was initially performed for unresectable CRLM primarily due to inadequate FLR<sup>[23]</sup>. Patients with tumors in the FLR were not included. Subsequently patients with tumors in the FLR were also operated on with a cleaning procedure of the FLR performed in stage I adopting from conventional TSH<sup>[14]</sup>. Apart from portal vein ligation and parenchymal partition, any tumor involvement of the FLR was resected. Provided tumor clearance of the FLR is feasible, bilobar CRLM was not considered a contraindication<sup>[47-49]</sup>. ALPPS has been reported for patients with extrahepatic diseases in small numbers<sup>[50,51]</sup>. The long term oncological outcomes require further validation. There is better acceptance for extrahepatic metastasis amendable to future surgical treatment<sup>[45]</sup>. After all, it complied with the principle of surgical oncology, *i.e.* to achieve R0 resection.

From registry data ALPPS achieved a 1- and 2-year OS of 76% and 62%, respectively for patients with CRLM. The corresponding 1- and 2-year DFS were 59% and 41%, respectively<sup>[3]</sup>. The tumor status and the proportion of patients receiving preoperative chemotherapy were not specified. Given the systemic disease nature, the importance of chemotherapy response could not be overemphasized. Chemotherapy response could be objectively defined with radiological and biochemical assessment<sup>[3]</sup>. Patients with favorable response to chemotherapy are more likely to secure disease control after local treatment. We learned from conventional TSH and standard liver resection that selection by chemotherapy response resulted in improved oncological outcomes<sup>[22,52]</sup>. Indeed, the pioneering surgeon of ALPPS suggested that ALPPS was not indicated for CRLM patients without prior chemotherapy<sup>[46]</sup>.

The major concerns for chemotherapy as well as targeted therapy were the potential drawbacks of reduced remnant growth and increased operative complications. Kremer *et al*<sup>[53]</sup> retrospectively compared eleven ALPPS patients who received preoperative chemotherapy with eight controls. It was observed that chemotherapy impaired remnant hypertrophy (FLR hypertrophy 59+/-22% vs 98+/-35%,  $P = 0.027$ ). There seemed to be no impact on operative morbidity and mortality. A safe time interval between chemotherapy and surgery has not been proposed. Experience from conventional hepatectomy showed that an interval shorter than 4 wk was associated with more surgical complications (11% vs 5.5/2.6% for 5-8/9-12 wk,  $P = 0.009$ )<sup>[54]</sup>. It is reasonable to wait for more than 4 wk for a more demanding ALPPS. While neoadjuvant chemotherapy selects patients with favorable tumor biology, the surgeon must be aware of its potential effects on ALPPS.

**Disease factor - hilar cholangiocarcinoma:** Hilar cholangiocarcinoma necessitates extensive parenchymal and biliary resection for tumor clearance. Not uncommonly, resection is hindered by inadequate FLR. Limited numbers of ALPPS has been performed for Klatskin tumor with much debate elicited for its safety. Patients with Klatskin tumor suffered from cholestasis and recurrent biliary sepsis both contributing to impaired hepatic regeneration<sup>[55]</sup> and increased septic complications<sup>[35]</sup>. Furthermore, tumor infiltration renders hilar dissection challenging. In fact, technical complexity in ALPPS has been closely associated with morbidity and mortality<sup>[56]</sup>. From registry data we learned that prolonged stage I operating time (more than 300 min) (OR = 4.42,  $P = 0.004$ ) and blood transfusion (OR = 5.26,  $P = 0.001$ ) were independent risk factors for severe complications<sup>[3]</sup>. When ALPPS was performed for Klatskin tumor, 90-d mortality was reported as an exceedingly high 48%<sup>[37]</sup>. In the study by Li *et al*<sup>[35]</sup>, bile leak and PHLF occurred more frequently in patients operated for hilar cholangiocarcinoma.

Oncological outcomes were also far from satisfactory. In a case-control study conducted by Olthof *et al*<sup>[37]</sup>, the median OS of cholangiocarcinoma patients undergoing ALPPS was 6 mo comparing unfavorably to matched controls with similar remnant volume and tumor status undergoing conventional hepatectomy (6 mo vs 27 mo,  $P = 0.06$ ). After all, the operative techniques of ALPPS conflicts with the oncological principles of bile duct cancer surgery. In the early periods hilar dissection was performed with complete lymphadenectomy of the hepatoduodenal ligament to allow clear identification of portal structures<sup>[2,57,58]</sup>. However, extensive portal dissection has been criticized for inducing segment IV ischemia and subsequent bile leaks<sup>[36]</sup>. Shifting away from extensive hepatoduodenal ligament dissection, lymphatic clearance could have been jeopardized. Nonetheless, there is no data in the literature to evaluate the adequacy of lymphatic clearance in ALPPS for bile duct cancers, and

further studies are warranted.

**Disease factor - HCC:** Vennarecci *et al*<sup>[59]</sup> reported the feasibility of ALPPS in chronic liver disease with their early experience in three HCC patients. Considering cirrhotic livers have diminished regenerative capacity, the safety profile may be different in this context. Two studies looked into the degree of hypertrophy, kinetic growth and operative outcomes among HCC patients in the international registry and from a Singaporean tertiary center, respectively<sup>[7,38]</sup> (Table 3). When compared to patients with normal liver, HCC patients consistently underwent less rapid (5%-19% FLR per day *vs* 9%-35% FLR per day) and less extensive hypertrophy (40%-47% *vs* 76%-138% increase in FLR). From 13 patients whose pathological details were available, both degree of hypertrophy (105%, 48%, 26% and 15% for grade 1, 2, 3 fibrosis and cirrhosis,  $P = 0.013$ ) and kinetic growth (12, 4.7, 3.0 and 1.5 mL/d for grade 1, 2, 3 fibrosis and cirrhosis,  $P = 0.033$ ) correlated directly with the degree of fibrosis<sup>[38]</sup>. Albeit comparing inferiorly to normal liver, ALPPS still induce substantial hypertrophy in fibrotic liver, especially when the degree of fibrosis is limited. In a recent series of 35 ALPPS performed in our center, the hypertrophy rate compared favorably to patients treated with PVE (5.1 mL/d *vs* 0.9 mL/d,  $P < 0.001$ )<sup>[60]</sup>. A median volume gain of 45.1% was achieved over a median interval of 6 d.

Pooled data from 35 patients in the international registry revealed a discouraging 31% mortality for patients with chronic liver disease<sup>[38]</sup>. However, more promising results have been produced in our center<sup>[60]</sup>. Thirty-five HCC patients started with a median FLR/ESLV ratio of 27%. All patients proceeded to stage II. Operative mortality was kept to 9% comparable to CRLM patients in the international registry<sup>[3]</sup>. These results indicated that chronic liver disease is not an absolute contraindication for ALPPS. Patients with low grade fibrosis are better candidates for the procedure, and a longer inter-stage interval is desirable to allow sufficient liver hypertrophy<sup>[61,62]</sup>. Vivarelli *et al*<sup>[63]</sup> suggested preoperative liver biopsy to determine the degree of liver fibrosis after observing a PHLF in a patient with fibrotic liver undergoing ALPPS. From our experience ALPPS candidates could be effectively selected by reviewing the surrogate markers reflecting the degree of liver fibrosis and portal hypertension, *i.e.* platelet count and indocyanine green clearance. Indocyanine green retention test correlated with the degree of portal hypertension<sup>[64,65]</sup> and mortality in major hepatectomy<sup>[66]</sup>. The role of indocyanine green clearance warrants further investigation to better understand its relationship with growth parameters and operative outcomes.

Not uncommonly, HCC is associated with portal venous invasion. When a tumor has invaded the right portal vein, PVE is neither technically feasible nor effective. Even PVL has little chance of further increasing the FLR volume as no further portal blood flow is redistributed. Alternatively, ALPPS could be a strategy to induce hypertrophy in HCC with portal tumor thrombus. Successful cases have been reported indicating technical feasibility<sup>[67,68]</sup>. An additional benefit conferred by ALPPS is the shortened inter-stage period. With a tumor thrombus in situ, disease is likely to progress while awaiting conventional second stage hepatectomy.

### Technical refinements

**Preservation of middle hepatic vein:** In the initial description of ALPPS, parenchymal partition was performed with division of the middle hepatic vein<sup>[2]</sup>. However, with significant morbidity observed following ischemic necrosis and bile leak, it was proposed that the middle hepatic vein could be preserved as the venous outflow of segment IV without jeopardizing parenchymal hypertrophy<sup>[69]</sup>. With a patent outflow, venous congestion and ischemia could be reduced. It has now become the preferred technique by most hepatobiliary surgeons. A questionnaire survey indicated that 70% surgeons routinely preserved the middle hepatic vein during ALPPS stage I<sup>[70]</sup>.

**Surgical management of hepatoduodenal ligament:** A complete hilar dissection and skeletonization of the hepatoduodenal ligament was performed in the classical approach to ALPPS. This allowed hilar vascular pedicles to be clearly identified but potentially contributed to complete devascularization of segment IV<sup>[36]</sup>. In the aforementioned questionnaire survey, 39% of the surgeons believed that skeletonization of the hepatoduodenal ligament was indicated<sup>[70]</sup>. Currently there is no consensus on the surgical approach to hepatoduodenal ligament. In ALPPS where lymphatic clearance is not indicated for oncological grounds, consideration can be given to limit hilar dissection to avoid potential detrimental effects on segment IV ischemia.

**Anterior approach:** The anterior approach to hepatectomy was initially proposed for bulky liver tumor with invasion of surrounding structures<sup>[71]</sup>. It entails portal pedicle division and complete parenchymal transection before right liver mobilization,



**Table 3** Associating liver partition with portal vein ligation for staged hepatectomy for hepatocellular carcinoma, *n* (%)

<i>n</i>	Tumor	FLR in mL		Hypertrophy		Kinetic growth in %/d	Severe Cx, ≥ IIIIB	PHLF, 50-50	90-d mortality	
		Stage I	Stage II	Absolute in mL	Relative in %					
Case control										
D'Haese <i>et al</i> <sup>[38]</sup> , 2016	35/225	HCC/CRL M	420 (346-540)/340 (260-433)	639 (541-855)/617 (487-724)	206 (172-277)/252 (186-348)	47 (26-69)/76 (50-108)	4.7 (2.8-8.9)/9.1 (5.8-14.3)	14 (27)/54 (17)	14 (40)/42 (19)	11 (31)/15 (7)
Chia <i>et al</i> <sup>[43]</sup> , 2018	9/4	HCC/non-HCC	381 (280-422)/313 (177-550)	-	154 (86-166)/251 (248-344)	40 (22-65)/138 (92-139)	19 (6-24)/35 (31-39)	1 (14)/0	2 (29)/1 (25)	1 (11)/0

CRLM: Colorectal liver metastasis; Cx: Complication; FLR: Future liver remnant; HCC: Hepatocellular carcinoma; PHLF: Post-hepatectomy liver failure.

minimizing bleeding and tumor spillage during the process. The concept of anterior approach has been adopted to ALPPS<sup>[72,73]</sup>. During stage I, hepatic parenchyma is split without prior right liver mobilization. In stage II, right liver is mobilized after division of right hepatic artery, bile duct and hepatic veins. In the setting of ALPPS, anterior approach could be more challenging given that the arterial and biliary pedicles had to be preserved during transection. Chan *et al*<sup>[73]</sup> prospective series of 13 patients indicated that complete parenchymal split was feasible and safe with anterior approach. Occurrence of perihepatic adhesions was minimized during stage II. Thirty-seven percent of the ALPPS procedures in the registry were performed using the anterior approach<sup>[74]</sup>. With reduced tissue manipulation tumor spillage was minimal. This was particularly important in the setting of ALPPS, where the tumor is left in torso during the inter-stage period. Further evaluation is required before any oncological benefit of anterior approach ALPPS could be ascertained. With the potential benefits the anterior approach appears to be the preferred procedure, especially when a bulky tumor is handled. Nevertheless, it would be rather challenging to combine a complex procedure with an advanced technical approach. Without reduced vascular control more difficult bleeding would be encountered during parenchymal transection. Anterior approach ALPPS is best reserved for hepatobiliary surgeons who excel in both ALPPS and anterior approach for conventional hepatectomy.

**Partial ALPPS:** Schlegel *et al*<sup>[75]</sup> concluded from canine model that accelerated regeneration in ALPPS was not solely related to redistribution of blood flow but also the presence of circulating factors secondary to tissue injury. Plasma levels of IL-6 were elevated after ALPPS, and injection of post-ALPPS plasma into mice treated with PVL produced comparable remnant hypertrophy. On this basis Petrowsky *et al*<sup>[76]</sup> proposed a technical modification of ALPPS with partial parenchymal partition, *i.e.* 50%-80% in an attempt to preserve collateral blood supply and reduce operative morbidity. The middle hepatic vein was preserved in stage I. Termed as partial ALPPS, the modified procedure was associated with zero mortality and a more favorable complication profile in the initial series of six patients<sup>[76]</sup>. Partial ALPPS effectively induced the same degree of FLR hypertrophy as a complete split (median hypertrophy 60% *vs* 61% in 7 d). The operative boundary for partial partition was subsequently defined as dissection to the level of middle hepatic vein as opposed to the inferior vena cava in complete ALPPS<sup>[77]</sup>.

However, the effectiveness of partial split appeared to be limited in chronic hepatitis. Chan *et al*<sup>[78]</sup> compared partial and complete ALPPS in 25 patients with HCC. Partial split failed to induce a similar degree of hypertrophy as in complete split (17.5 mL/d *vs* 31.2 mL/d, *P* = 0.022). Perioperative morbidity and mortality were not decreased. After all, current evidence is based on limited experience and partial ALPPS could be further validated in larger cohorts. Perhaps partial ALPPS is most effective when liver function is normal, and a complete split is technically difficult. When a sizable tumor is situated close to the middle hepatic vein or inferior vena cava, parenchymal transection to the vena cava could be impeded by troublesome bleeding from engorged hepatic veins<sup>[78]</sup>. Partial ALPPS potentially reduced bleeding and subsequent complications. The difficult transection is probably better tolerated in stage II when the remnant has undergone hypertrophy and the procedure is expedited after full mobilization of the right liver and division of the arterial and biliary pedicles. Slower hypertrophy and delayed stage II operation are the potential drawbacks.

## CONCLUSION

ALPPS challenged the concept of unresectability and stretched the limit of liver surgery. When performed for CRLM, ALPPS was associated with similar mortalities and morbidities as with TSH. Mortality is usually a result of PHLF, and it can be minimized with careful patient selection. The benefit of ALPPS is maximized when performed for young patients with very borderline remnant volume. Various technical modifications have been proposed to improve the surgical outcomes of ALPPS. Preservation of the middle hepatic vein during stage I minimized morbidities and did not affect remnant growth. In patients with challenging anatomy, partial ALPPS potentially reduces morbidity but remnant hypertrophy may compare unfavorably to a complete split. Whether the theoretical advantages of ALPPS translate to actuarial survival benefits warrants further studies.

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