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ALPPS Offers a Better Chance of Complete Resection in Patients with Primarily Unresectable Liver Tumors Compared with Conventional-Staged Hepatectomies: Results of a Multicenter Analysis

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Abstract

Background Portal vein occlusion to increase the size of the future liver remnant (FLR) is well established, using portal vein ligation (PVL) or embolization (PVE) followed by resection 4–8 weeks later. Associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) combines PVL and complete parenchymal transection, followed by hepatectomy within 1–2 weeks. ALPPS has been recently introduced but remains controversial. We compare the ability of ALPPS versus PVE or PVL for complete tumor resection.

Methods A retrospective review of all patients undergoing ALPPS or conventional staged hepatectomies using PVL or PVE at four high-volume HPB centres between 2003 and 2012 was performed. Patients with primary liver tumors and liver metastases were included. Primary endpoint was complete tumor resection. Secondary endpoints include 90-day mortality, complications, FLR increase, time to resection, and tumor recurrence.

Results Forty-eight patients with ALPPS were compared with 83 patients with conventional-staged hepatectomies. Eighty-three percent (40/48 patients) of ALPPS patients achieved complete resection compared with 66 % (55/83 patients) in PVE/PVL (odds ratio 3.34, $p = 0.027$). Ninety-day mortality in ALPPS and PVE/PVL was 15 and 6 %, respectively ($p = 0.2$). Extrapolated growth rate was 11 times higher in ALPPS (34.8 cc/day; interquartile range (IQR) 26–49) compared with PVE/PVL (3 cc/day; IQR2-6; $p = 0.001$). Tumor recurrence at 1 year was 54 versus 52 % for ALPPS and PVE/PVL, respectively ($p = 0.7$).

Conclusions This study provides evidence that ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumors at the cost of a high mortality. The technique is promising but should currently not be used outside of studies and registries.

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Introduction

Resection of a large tumor load in the liver may result in an excessive removal of hepatic parenchyma leading to post-operative liver failure and associated complications [1]. This has led to the use of portal vein manipulations to increase the size of the putative future liver remnant (FLR). Multiple modifications have been described including a variety of two-stage surgeries combining removal of tumors from the FLR with portal vein embolization (PVE) [2, 3] or concomitant portal vein ligation (PVL) [1, 4] as well as PVE followed by extended right hepatectomy.

A new variant of portal vein occlusion associated with staged hepatectomy was recently described to enhance volume increase of the FLR [5]. This approach combines liver partition with PVL followed by a second operation to remove the deportalized, diseased part of the liver. The acronym "ALPPS" (Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy) has been proposed to describe this complex procedure [6]. Initial experience suggested that the volume increase after ALPPS is more rapid compared with previous techniques allowing removal of the diseased part of the liver within only 1–2 weeks after liver partition [5, 7]. Several other groups have subsequently described the feasibility of ALPPS [8–10], and the procedure was rapidly implemented by many to attempt curative liver resection in patients with small FLRs. Despite its potential to induce rapid volume increase, ALPPS may be associated with higher postoperative morbidity and mortality rates [5, 8]. An editorial and several letters to the *Annals of Surgery* have sparked a controversy over the benefits and dangers of the ALPPS procedure [11–17].

Both PVE and PVL carry a considerable failure rate, because only about two thirds of patients may eventually benefit from a subsequent curative resection due to tumor progression during the waiting interval between the two stages or failure of the FLR to grow [2, 4, 18–20]. While some consider tumor progression in the waiting interval as a useful selection tool to avoid an extensive liver resection in patients with unfavourable tumor biology [14], others hypothesized that the long time interval between the two stages rather than tumor biology is responsible for the high degree of disease progression between stages [5–9, 21]. Recently, proponents of PVE have compared their own results with the inaugural German series to argue against the innovation [22]. Conclusive evaluations of overall and disease-free survival comparing the two techniques will require large patient populations, which are currently not yet available. The purpose of this study therefore was to compare the ability of ALPPS versus conventional two-stage approaches (using PVL or PVE) to achieve complete tumor resection using a short-time endpoint instead, allowing for appropriate sample size and avoidance of single-centre bias by using a multicenter design.

Materials and methods

Primary endpoint

The primary endpoint was reached when the second stage was performed with resection of the entire tumor load with free margins in the pathology specimen. The sample size of patients necessary to answer the question whether ALLPS was better than PVE/PVL to achieve complete tumor resection was based on literature data suggesting nonprogression to the second stage and thereby failure of the entire strategy in up to a third of patients in PVE/PVL [2, 4, 8, 18, 19] and in nearly no patients for ALPPS [5, 7]. Assuming a power of 0.8 and α-error of 0.05, more than 40 patients were needed in each arm. Therefore, four international centers (Zurich, Switzerland; London, Ontario, Canada; Buenos Aires, Argentina; Mainz, Germany) with experience with the ALPPS procedure collaborated to pool more than 40 consecutive ALPPS and PVE/PVL patients in each arm. Patients who failed the primary endpoint were classified according to four patterns of failure: (A) perioperative death, (B) no stage 2 because of tumor progression, (C) no stage 2 because of failure to grow, (D) incomplete resection (R1).

Patients

All consecutive patients, who underwent ALPPS performed between January 2011 and September 2012 in the four collaborating centres, were compared with all patients who underwent conventional approaches (PVE/PVL) performed between January 2003 and September 2012 in the same centres. Patients presenting with major extrahepatic surgery or subjected to selective intra-arterial chemotherapy and those with incomplete data on liver volumetry or lost to follow-up were excluded. An institutional review board (IRB) approval was obtained in each center.

Surgical technique

The surgical technique for ALPPS and conventional two-stage liver resections associated with PVE or PVL have been described elsewhere [5, 7]. In brief, for ALPPS, stage 1 consists of tumor clearance of the FLR in case of multifocal bi-lobar tumors followed by parenchymal transection between the FLR and the diseased part of the liver with concomitant selective PVL. In cases of single large central tumors, transection with PVL is performed only.

In the PVL group, the FLR is cleared of tumor and the portal vein to the diseased hemi-liver is ligated during the first stage without concomitant parenchymal transection, in contrast to ALPPS. In the PVE group, patients undergo percutaneous PVE with coils or histoacryl/lipiodol, either alone (in case of unilobar disease) or 1–2 weeks after tumor clearance of the FLR in patients with multifocal bilobar tumors. In PVE and PVL, the diseased deportalized part of the liver is removed 4–8 weeks later.

Liver volumetry

For all groups, baseline FLR volume (FLR1, i.e., before stage 1) and volume before stage 2 (FLR2) were measured by computer tomography (CT) or magnetic resonance imaging (MRI) using dedicated volume rendering software [23, 24]. To standardize the speed of volume increase between the two groups, a mean volume increase per day was calculated. Since time intervals between stages differed between ALPPS and PVE/PVL, this assessment of kinetic growth was considered an approximation. Standardized total liver volume (sTLV) was calculated according to Vauthey [25]. The Mosteller formula was used to calculate body surface area. Standardized FLR1 (sFLR1) and sFLR2 were calculated accordingly as FLR1/sTLV*100 % and FLR2/sTLV*100 %, respectively.

Secondary endpoints

Secondary endpoints included: 90-day mortality, overall and severe complications, comprehensive complication index (CCI) [26], postoperative liver and renal failure, and tumor recurrence up to 12 months. The study was not powered to detect differences in secondary endpoints. Complications were recorded using the Clavien-Dindo classification [27]; a severe complication was defined as grade $\geq$ IIIB (requirement of invasive procedures under general anesthesia to correct a complication). The novel CCI was reported to summarize for the first time all postoperative complications and their severities over both stages into one single continuous scale (www.assessurgery.com) [26]. Postoperative liver failure was defined according to the 50/50 criteria [28], renal failure as an increase of creatinine within 48 h after surgery to more than 1.4 of the preoperative level [29]. Tumor progression and recurrence were assessed up to 12 months starting to count from the first stage in both arms.

American Society of Anesthesiologists (ASA) physical status classification system was coded based on the definition provided on the ASA webpage (www.asahq.org). Charlson score was determined using a Microsoft® Excel macro [30]. Type of tumor and histology was coded based on pathology source documents. Tumor size and number of lesions were defined through primary review of imaging by experienced radiologists in each center.

Statistical analysis

The distribution of variables was analyzed using means and standard deviation (SD) for normally distributed, and median and interquartile ranges (IQR) for nonnormally distributed data. Data were tested for normality using quantile–quantile plots of dependent variables.

The primary endpoint (*complete resection with R0 margins)* was compared between the two groups (ALPPS vs. PVE/PVL) using uni- and multivariate logistic regression models with the primary endpoint as the dependent and treatment group as the independent variable. We adjusted for following potential confounders: age, previous abdominal surgery (yes/no), type of tumor, FLR1/body weight (BW), and liver macrosteatosis (yes/no). Uni- and multivariate linear as well as logistic regression analyses were performed for the secondary endpoints. Data were reported as point estimates, 95 % confidence intervals (CI), and p values ($\leq$0.05 considered as significant).

Kaplan–Meier survival curves were constructed for time to proceed to the second stage and progression free survival. Associating liver partition with portal vein ligation for staged hepatectomy and PVE/PVL were compared using log-rank statistics.

All statistical analyses were performed using STATA 11 (Stata Corp., College Station, TX). Figures were made using Graph Pad Prism (Graph Pad Software, La Jolla, CA).

Results

A total of 170 patients with liver tumors undergoing liver resections in two stages at the four centres were analyzed. Thirty-nine patients were excluded because of simultaneous extrahepatic surgery ($n = 4$), placement of selective intra-arterial perfusion pumps ($n = 14$), had benign tumors ($n = 7$), had no appropriate imaging ($n = 13$), or were lost to follow-up within 3 months ($n = 1$). A total of 131 patients were eventually included: 48 with ALPPS and 83 with PVE/PVL (Fig. 1).

Comparison of patient population demographics, morbidity, and comorbidity data showed a higher percentage of mild hepatic macrosteatosis (<30 %) in the ALPPS group as well as difference in the number of enrolled patients per centre (Table 1). Future liver remnant in cubic centimetres and sFLR in percent before stage 1 (FLR1 and sFLR1), as well FLR to body weight ratio before stage 1 (FLR1/BW) were not statistically different between both groups. Need for biliary reconstruction was higher in ALPPS in stage 1 and higher in PVE/PVL in stage 2, but in both stages, comparable (Table 2).

Eighty-three percent (40/48) of ALPPS patients achieved complete resection compared with 66 % (55/83) in the PVE/PVL group. Seventeen percent (8/48) of ALPPS patients failed the primary endpoint due to (A) mortalities ($n = 7$) and due to one patient with (D) incomplete resection (R1) (Table 3).

In comparison, 28 of 83 patients (34 %) in the PVE/PVL group did not reach complete resection because of

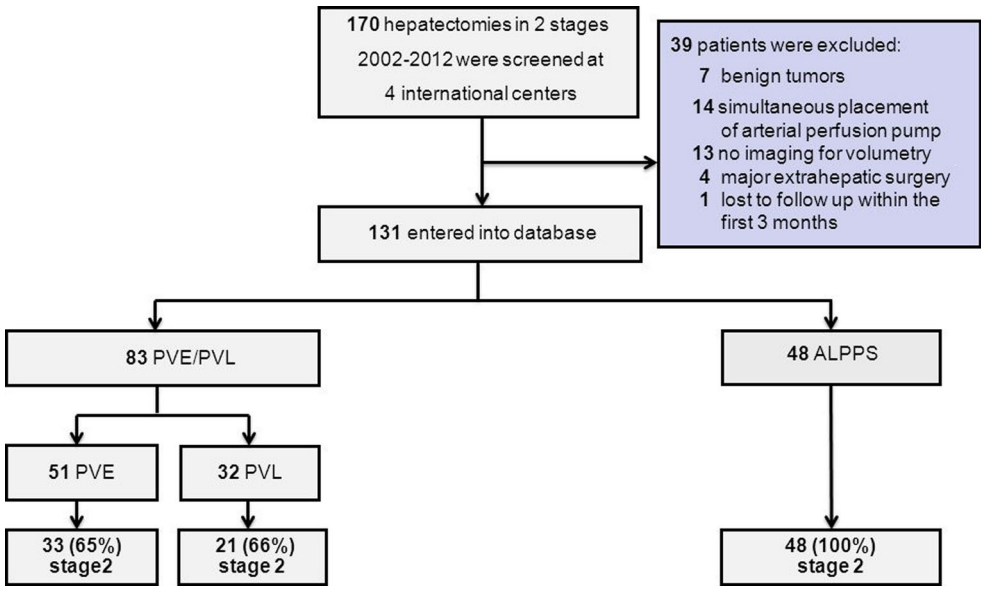

Fig. 1 Flowchart of patients screened and included in the study

(A) postoperative mortality ($n = 5$), (B) liver ($n = 4$) or systemic ($n = 9$) tumor progression, (C) failure of the FLR to grow ($n = 6$) and R1 resection in 4 patients (Table 3). Results of the multivariate analysis for primary and secondary endpoints and the odds ratios of patients with ALPPS for these endpoints, unadjusted and adjusted for age, previous abdominal surgery, type of tumor, FLR1/BW, and liver macrosteatosis are shown in Table 4; ALPPS was more likely to achieve complete resection (adjusted OR 3.34, CI 1.15-9.74, $p = 0.027$).

Mortality at 90 days was 15 % (7/48) in ALPPS compared with 6 % (5/83) in PVE/PVL, i.e., the corrected odds for perioperative death were 2.7 time higher ($p = 0.2$; Table 4). Severe complications were more common in ALPPS after both steps compared with PVE/PVL, but the numbers were too small to show significance. In both groups, liver failure occurred only after stage 2 at 13 and 9 % in ALPPS and PVE/PVL, respectively. There was a trend towards more overall complications in the ALPPS group according to the new CCI ($p = 0.05$). There were no differences in the incidence of postoperative bile leaks. The incidence of acute renal failure after stage 1 in ALPPS seemed high at 8 % (4/48), but renal failure after stage 2 was not different between groups at 10 and 15 % for ALLPS and PVE/PVL, respectively (Table 4).

Median FLR2, sFLR2, and FLR2/BW (i.e., before stage 2) were higher in ALPPS than in PVE/PVL (Table 5). Each ALPPS patient reached the 30 % sFLR cutoff recommended for safer liver surgery [1] before stage 2, whereas many PVE/PVL cases did not (Fig. 2). Increase of FLR volume between stage 1 and 2 in both groups was significant ($p \leq 0.001$) (Fig. 2). The median increase of FLR between stages was 34 % for PVE/PVL and 77 % for ALLPS (Table 5). Extrapolated kinetic growth for ALPPS was 11 times higher (34.8 cc/day, IQR 26.4–48.5) compared with PVE/PVL (2.78 cc/day, IQR 1.69–5.81; Fig. 2; Table 5).

Whereas ALPPS patients proceeded to resection faster (Fig. 3a), tumor recurrence occurred at a comparable rate in both groups at 12 months with 54 % in ALPPS and 52 % in PVE/PVL (Fig. 3b).

Discussion

Patients with primarily unresectable liver tumors have a poor prognosis with a near zero 5-year survival despite the availability of modern chemotherapy. Because only a curative resection offers a chance of long-term survival, strategies using staged hepatectomies have been developed over the past two decades, however, with limited success [2, 4, 18, 19]. It has been suggested that the recently introduced ALPPS procedure offers new horizons to remove extensive tumors localized to the liver by stimulating regeneration of the healthy part of the liver at an unprecedented pace and extent [5, 6]. This enthusiasm has been challenged by others due to lack of convincing data and fear of an increased rate of perioperative complications [12, 14].

While definitive evidence for a long-term benefit in survival of ALPPS will be lacking for a long time due to the large numbers of patients necessary to show a difference, it is critical to evaluate this approach before it is widely used or abandoned without objectively weighing its merits. While an attempt has been made to compare PVE to the published data about ALPPS [22], no large comparative study is currently

Table 1 Characteristics of patients with unresectable liver tumors cohorts undergoing PVE/PVL or ALPPS

Characteristics	PVE/PVL group Stage 1: $n = 83$ Stage 2: $n = 54$	ALPPS group In stage 1: $n = 48$ In stage 2: $n = 48$	p value
Age (year)	61 (54–69)	57 (48.5–65)	0.11
Sex, male/female	57 (68.7 %)/26 (31.3 %)	29 (60.4 %)/19 (39.6 %)	0.34
ASA			0.07
≤2	57 (68.7 %)	40 (83.3 %)	
>2	26 (31.3 %)	8 (16.7 %)	
Charlson index	7 (6–9)	8 (4–9)	0.47
Diabetes mellitus	11 (13.3 %)	4 (8.3 %)	0.4
Type of tumor			0.68
CRLM	48 (57.8 %)	26 (54.2 %)	
HCC	7 (8.4 %)	3 (6.3 %)	
Biliary carcinoma	16 (19.3 %)	10 (20.8 %)	
IHCC	5 (6 %)		
PHCC	11 (13.2 %)	2 (4.2 %)	
Other malignant tumors	12 (14.5 %)	7 (14.6 %)	
BMI (kg/m^2)	25.4 (23.1–28.7)	25.9 (23.4–28.8)	0.95
Preoperative chemotherapy	44 (53 %)	28 (58.3 %)	0.56
Creatinine baseline (μmol/L)	71 (62–86)	71 (62–82.2)	0.49
Bilirubin baseline (μmol/L)	12 (8–20)	11 (6.6–15.7)	0.09
INR baseline	1 (1–1.1)	1 (1–1.1)	0.52
Preoperative biliary drainage			
In stage 1	11 (13.3 %)	4 (8.3 %)	0.44
In stage 2	12 (22.2 %)	5 (10.4 %)	0.27
Previous liver surgery	16 (19.3 %)	9 (18.8 %)	0.94
Multifocal bilobar tumor	56 (67.5 %)	29 (60.4 %)	0.42
Number of lesions			
<5	50 (60.2 %)	23 (47.9 %)	0.09
≥5	29 (34.9 %)	25 (52.1 %)	
Missing	4 (4.9 %)	0 %	
Histology			
No histology	29 (34.9)	–	
Normal	25 (30.2 %)	17 (35.4 %)	0.10
Macrosteatosis			
>30 %	8 (9.6 %)	2 (4.2 %)	0.026
<30 %	17 (20.5 %)	21 (43.7 %)	0.35
Fibrosis	4 (4.8 %)	6 (12.5 %)	–
SOS	0 %	2 (4.2 %)	–
CASH	0 %	0 %	
Centers			
Zurich, CH	40 (48.2 %)	18 (37.5 %)	0.24
London Ontario, CA	21 (25.3 %)	5 (10.4 %)	
Buenos Aires, AR	12 (14.5 %)	15 (31.3 %)	
Mainz, GE	10 (12 %)	10 (20.8 %)	

All data are given in proportions or in medians with interquartile ranges (IQR)

PVE/PVL portal vein embolization/portal vein ligation, *ALPPS* associating liver partition with portal vein ligation for staged hepatectomy, *ASA* American Society of Anesthesiologists Physical Status Classification, *BMI* body mass index, *INR* international normalized ratio, *CRLM* colorectal liver metastasis, *HCC* hepatocellular carcinoma, *IHCC* intrahepatic cholangiocarcinoma, *PHCC* perihilar cholangiocarcinoma, *SOS* sinusoidal obstruction syndrome, *CASH* chemotherapy-associated steatohepatitis, *CH* Switzerland, *CA* Canada, *AR* Argentina, *GE* Germany

available. At this point, centres have reported small case series, mostly with a focus on feasibility and technical variations, such as the description of a laparoscopic approach [16], providing only anecdotal information. Therefore, we designed a study with the endpoint complete resection, which is a relevant and sufficiently powered, short-term

Table 2 Operative characteristics of patients with unresectable liver tumors cohorts undergoing PVE/PVL or ALPPS

Stage 1	PVE/PLV group $n = 83$	ALPPS group $n = 48$	p value
Type of surgery			
PVO	83 (100 %)		
PVE	51 (62.4 %)		
PVL	32 (38.6 %)		
ALPPS	–	48 (100 %)	
Size of FLR1 (cc)	389 (324–470)	367 (286–440)	0.10
Size of sFLR1	0.24 (0.18–0.31)	0.23 (0.18–0.29)	0.07
FLR1/BW (cc/kg)	0.53 (0.39–0.67)	0.47 (0.39–0.59)	0.06
Cleaning of the FLR	55 (66 %)	28 (58.3)	0.27
Biliary reconstruction	0 (0 %)	8 (16.7 %)	<0.001
Hepaticojejunostomy			
One duct		5	
Multiple ducts		3	
Stage 2	**PVE/PVL group $n = 54$**	**ALPPS group $n = 48$**	**p value**
Size of FLR2 (cc)	530 (454–648)	639 (525–786)	0.007
Size of sFLR2	0.35 (0.27–0.45)	0.41 (0.34–0.47)	0.003
FLR2/BW (cc/kg)	0.73 (0.56–0.96)	0.84 (0.73–0.99)	0.005
Biliary reconstruction	15 (27.8 %)	4 (8.3 %)	0.06
Hepaticojejunostomy			
One duct	9	2	
Multiple ducts	6	2	

All data are given in proportions or in medians with interquartile ranges (IQR)

PVO portal vein occlusion, *PVE/PVL* portal vein embolization, portal vein ligation, *ALPPS* associating liver partition with portal vein ligation for staged hepatectomy, *FLR1* future liver remnant volume prior to stage 1, *FLR2* future liver remnant volume prior to stage 2, *sFLR1* standardized future liver remnant prior to stage 1, *sFLR2* standardized future liver remnant prior to stage 2, *FLR1/BW* future liver remnant to body weight ratio prior to stage 1, *FLR2/BW* future liver remnant to body weight ratio prior to stage 2

Table 3 Reasons for failure of the primary endpoint

Reason for failure	PVE/PVL $n = 83$	ALPPS $n = 48$
A. Perioperative death (3 months) n (%)	5 (6 %)	7 (15 %)
B. No stage 2 because of tumor progression n (%)	13 (16 %)	0
Liver n	4	0
Systemic n	9	0
C. No stage 2 because of failure to grow n (%)	6 (7 %)	0
D. Incomplete resection (R1) n (%)	4 (5 %)	1 (2 %)
Patients who failed primary endpoint n (%)	28 (34 %)	8 (17 %)

surgical endpoint. The only chance of cure for this high-risk population, which often is offered only palliative chemotherapy, is a complete extirpation of the tumor, which requires staged procedures combining PVE or PVL and major hepatectomy at a later stage. This endpoint was chosen because achieving early complete resection is the indisputable basis for long-term survival.

The putative advantage of ALPPS is a faster regeneration of the FLR, which enables surgeons to proceed with the second stage before the development of adhesions or tumor progression. This key feature of ALLPS has been questioned by a few proponents of PVE, who claimed that the volume increase observed in ALPPS is similar to what can be achieved after right PVE, particularly with the

Table 4 Clinical outcomes of the two patient cohorts using logistic and linear regression analysis correcting for important confounders

	PVE/PVL group In stage 1: $n = 83$ In stage 2: $n = 54$ (proportion)	ALPPS group In stage 1: $n = 48$ In stage 1: $n = 48$ (proportion)	Unadjusted odds ratio (95 % CI, p value)	Adjusted odds ratio (95 % CI, p value)
Primary endpoint				
Complete resection (R0)	55 (66.3 %)	40 (83.3 %)	2.55 (1.05–6.17, $p = 0.039$)	3.34 (1.15–9.74, $p = 0.027$)
Secondary endpoints				
In-hospital mortality after stage 1	0 %	0 %	–	–
In-hospital mortality after stage 2	2 (3.7 %)	7 (14.6 %)	4.4 (0.9–22.5, $p = 0.072$)	2.47 (0.34–17.45, $p = 0.368$)
90-day mortality	5 (6 %)	7 (14.6 %)	2.66 (0.8–8.9, $p = 0.112$)	2.65 (0.6–11.9, $p = 0.201$)
Any complication after stage 1	21 (25.3 %)	21 (43.8 %)	2.3 (1.08–4.89, $p = 0.031$)	2.16 (0.86–5.46, $p = 0.103$)
Any complication after stage 2	40 (74.1 %)	35 (72.9 %)	0.95 (0.39–2.29, $p = 0.907$)	0.64 (0.22–1.84, $p = 0.407$)
Severe complications (≥IIIB) after stage 1	2 (2.4 %)	7 (14.6 %)	6.9 (1.4– 34.8, $p = 0.019$)	–
Severe complications (≥ IIIB) after stage 2	8 (14.8 %)	13 (27.1 %)	2.13 (0.8–5.7, $p = 0.131$)	2.0 (0.6–6.5, $p = 0.238$)

	PVE/PVL group In stage 1: $n = 83$ In stage 2: $n = 54$ Median (IQR)	ALPPS group In stage 1: $n = 48$ In stage 2: $n = 48$ Median (IQR)	Unadjusted difference (95 % CI, p value)	Adjusted difference (95 % CI, p value)
Comprehensive complications index (CCI) for both stages	20.9 (8.7–30.8)	26.2 (8.7–44.9)	10.9 (−0.3 to 22.0, $p = 0.057$)	11.5 (−0.2 to 23.3, $p = 0.054$)

	PVE/PVL group In stage 1: $n = 83$ In stage 2: $n = 54$ (proportion)	ALPPS group In stage 1: $n = 48$ In stage 1: $n = 48$ (proportion)	Unadjusted odds ratio (95 % CI, p value)	Adjusted odds ratio (95 % CI, p value)
Postoperative liver failure after stage 1[a]	0 %	0 %	–	–
Postoperative liver failure after stage 2[a]	5 (9.3 %)	6 (12.5 %)	1.3 (0.4–4.9, $p = 0.651$)	1.1 (0.2–4.5, $p = 0.934$)
Bile leak after stage 1	2 (2.4 %)	1 (2.1 %)	–	–
Bile leak after stage 2	9 (16.7 %)	10 (20.8 %)	1.3 (0.5–3.6, $p = 0.59$)	1.3 (0.4–4.0, $p = 0.685$)
Acute kidney failure after stage 1	2 (2.4 %)	4 (8.3 %)	–	–
Acute kidney failure after stage 2	8 (14.8 %)	5 (10.4 %)	0.7 (0.2–2.2, $p = 0.508$)	0.35 (0.1–1.8, $p = 0.2$)

Data are reported as proportion or medians with IQR, differences as point estimates with 95 % confidence intervals (CI) and p values (≤0.05 considered as significant)

Adjusted for age, previous abdominal surgery (non-liver), different diseases, FLR1/BW (prior to stage 1), and liver steatosis (yes/no). No statistical analysis if less than 5 patients

[a] By 50–50 criteria, see "Materials and methods" Section

Table 5 Analysis of volume changes in patients undergoing ALPPS and PVE/PVL using linear regression analysis

	PVE/PVL group In stage 1: $n = 83$ In stage 2: $n = 54$ Median (IQR)	ALPPS group In stage 1: $n = 48$ In stage 2: $n = 48$ Median (IQR)	Unadjusted difference (95 % CI, p value)	Adjusted difference (95 % CI, p value)
FLR2 (before stage 2) (cc)	530 (454–648)	638.5 (525–785.5)	93.7 (19.9–167.6, $p = 0.013$)	130.9 (61.7–200.1, $p < 0.001$)
sFLR2 (before stage 2)	0.35 (0.27–0.45)	0.41 (0.34–0.47)	0.05 (0.01–0.09, $p = 0.019$)	0.08 (0.05–0.11, $p < 0.001$)
FLR2/BW ratio before stage 2 (cc/kg)	0.73 (0.56–0.96)	0.84 (0.73–0.99)	0.1 (0.003–0.19, $p = 0.042$)	0.18 (0.11–0.25, $p < 0.001$)
Increase of FLR between stage 1 and 2 (%)	34.1 (17.4–55.7)	77.4 (52.8–101.7)	46.5 (33.8–59.2, $p < 0.001$)	42 (30.1–53.9, $p < 0.001$)
Extrapolated kinetic growth (cc/day)	2.78 (1.69–5.81)	34.8 (26.4–48.5)	34.4 (30.2–38.6, $p < 0.001$)	34 (29.4–38.5, $p < 0.001$)

Data are reported as medians with IQR, differences as point estimates with 95 % confidence intervals (CI) and p values (≤ 0.05 considered as significant)

Adjusted for age, previous abdominal surgery (non-liver), different diseases, FLR1/BW (prior to stage 1) and liver steatosis (yes/no). All results are reported as median and interquartile range

FLR2 future liver remnant prior to stage 2, *sFLR2* standardized future liver remnant prior to stage 2, *FLR2/BW ratio* future liver remnant divided by body weight prior to stage 2

inclusion of segment four [14]. The results of this comparative analysis of 131 cases provide overwhelming evidence for a higher degree of liver regeneration with the ALPPS procedure, as previously suggested in small case series [5, 7, 8]. Of course, the limitation of our standardization of kinetic growth is the fact that is based on different time periods between stages as the denominator in ALPPS and PVE/PVL, shorter in ALPPS, longer in PVE/PVL. However, this study contributes to the evidence that rapid hypertrophy in ALPPS is real.

It has been challenged that reduced waiting time to proceed with complete resection may represent an oncological advantage. Several clinicians have argued that a long waiting interval in the conventional approaches is rather a selection tool to identify those who may best benefit from the completion hepatectomy [14]. Another concern raised was that livers are strongly manipulated in the ALPPS procedure, which may promote tumor cell dissemination by detaching cells into the systemic and pulmonary circulation. Additionally, the local and systemic release of growth factors may further stimulate tumor growth [14]. This study does not corroborate such concerns at least in the short-term, because recurrence occurred at a similar rate in both groups.

In the inaugural manuscript from Germany, ALPPS was successful in achieving complete resection at the cost of a postoperative mortality rate of 12 % (3/25) [5], which is also in the range of the mortality observed in this study. While these figures are undoubtedly high, it is difficult to define what is acceptable mortality in a population presenting with such advanced malignancies and the potential

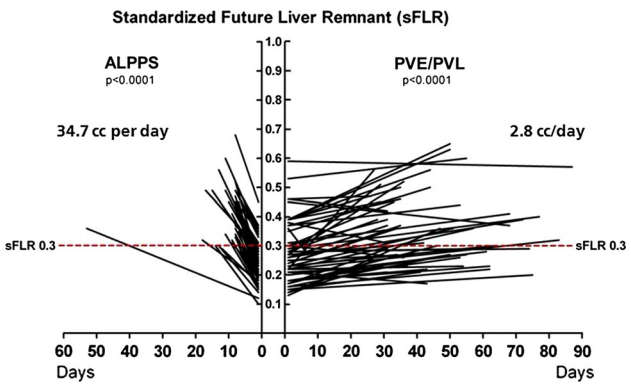

Fig. 2 Extrapolation of kinetic growth by depicting the increase of the standardized future liver remnant volumes (sFLR) determined by volumetry before stage 1 (*middle*) and before stage 2 in ALPPS (*left*) and PVE/PVL (*right*). The *interrupted line* shows the common clinical cutoff of 30 % for safer liver surgery

for a curative surgical approach. Postoperative mortality has to be balanced with the risk of incomplete resection using the conventional approaches or in some cases the lack of alternative therapies in cases when the FLR is extremely small. Staged hepatectomies, including PVE or PVL, are associated with a postoperative mortality rate between 6 and 8 % [2, 4, 18, 19] compared with a 3–6 % mortality rate for conventional major hepatectomies [31]. The mortality of PVE/PVL in this series of 5 of 83 (6 %) is within the reported range. The 90-day mortality of 14.6 % in our cohort represents the initial experience with the ALPPS operation and, without any doubt, includes our

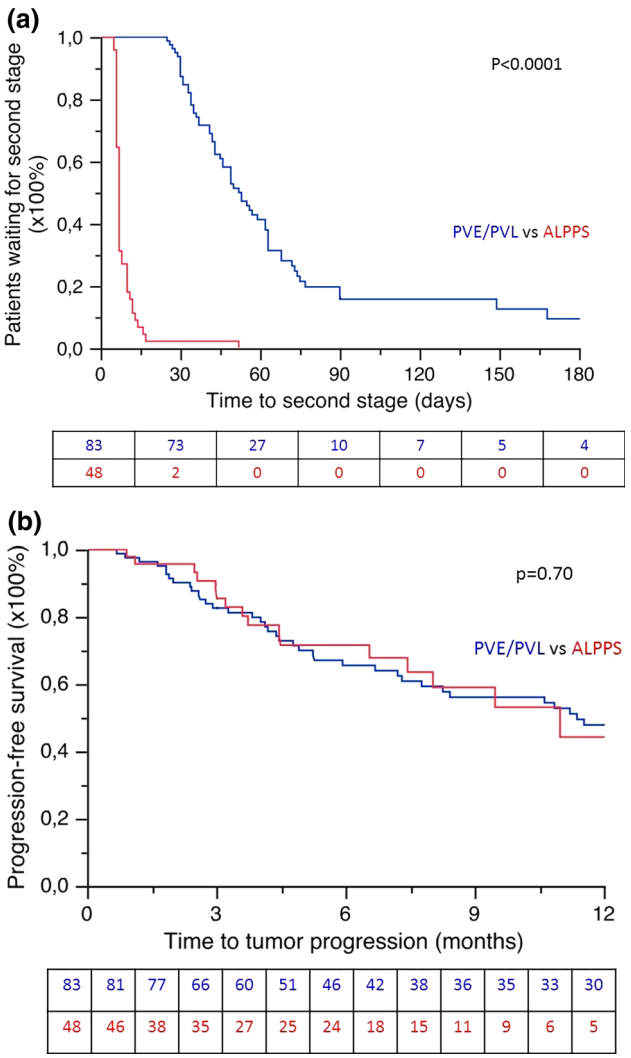

Fig. 3 **a** Kaplan–Meier graph demonstrating progression to stage 2 surgery comparing ALLPS with PVE/PVL. Numbers of patients at risk in the *bottom line*. **b** Kaplan–Meier graph demonstrating time to progression or recurrence or persistence of tumor after resection comparing ALLPS with PVE/PVL. Numbers of patients at risk in the *bottom line*

learning curve. In addition, this cohort inevitably has a selection bias, because patients may have been offered ALPPS because they were deemed inoperable by a conventional two-stage approach.

Liver failure, abdominal sepsis, and biliary leaks after surgery were the leading causes for severe complications and death in both groups, which is not different to what has been observed after conventional liver surgery [32]. Severe complications were rare after stage 1 in PVE/PVL, but occurred both after stage 1 and stage 2 in ALPPS. A risk factor analysis for complications failed to identify significant risk factors, probably due to the small sample size, although, of interest, five of seven fatalities in the ALPPS group occurred in patients older than 70 years of age and

Table 6 Recommendations for ALPPS

1. Best indication is a large tumor load with marginal future liver remnant (FLR) and curative intent
2. Should be used with caution in patients older than 70 years
3. Should be used with caution in patients with primary liver tumors (HCC, CCC)
4. Surgical team should have experience in complex liver surgery
5. Experience with in situ split or live donor liver transplantation might be of benefit
6. Avoid concomitant major abdominal surgery such as pancreatectomies and rectal resection
7. Informed consent mentioning higher perioperative morbidity and mortality should be obtained
8. Registration of patients in an international registry (www.alpps.net)
9. Should be preferentially performed in the setting of a prospective trial

five of seven fatalities occurred in patients with primary liver tumors. Considering the high morbidity and mortality, we caution the application of ALPPS as summarized in Table 6. With later knowledge and technical developments, revisions of these recommendations will become necessary.

This study is not without limitations. For example, the retrospective methodology yields a bias in the selection of patients in each group. ALPPS was chosen in an attempt to offer a curative operation to patients with extended liver malignancies, who had few options, but were interested in an aggressive, potentially curative, surgical approach. Also the time periods of patient inclusion differed, which is frequently unavoidable when new technologies are evaluated. However, we meticulously included all approaches involving the induction of liver hypertrophy by portal vein occlusion performed in the respective time periods at the respective centres. To address the concern about selection bias, we performed a multivariate analysis adjusting for known confounders. Secondly, the size of groups allowed us to evaluate our primary endpoint but did not provide enough power to convincingly address the differences in overall and disease-free survival, as well as morbidity. Finally, the majority of cases were performed very recently without sufficiently long follow-up to report long-term oncological results.

In conclusion, this study suggests that ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumors. This approach deserves further evaluation. Therefore, we implemented a registry (www.alpps.net) and initiated a multicenter RCT (www.clinicaltrials.gov; NCT 01775267). For the time being, due to the higher risk of morbidity and fatalities, we caution the widespread application of ALPPS outside of experienced centres.

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