Surgery 000 (2018) 1–8

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

# Indicating ALPPS for Colorectal Liver Metastases: A Critical Analysis of Patients in the International ALPPS Registry

Andreas A. Schnitzbauer[a,1,*], Erik Schadde[b,1], Michael Linecker[c], Marcel A. Machado[d], Rene Adam[e], Massimo Malago[f], Pierre A. Clavien[c], Eduardo de Santibanes[g], Wolf O. Bechstein[a]

[a] University Hospital Frankfurt, Goethe-University Frankfurt/Main, Clinic for General and Visceral Surgery, Germany
[b] Rush University Medical Center, Department of Transplant Surgery, Department of Surgery, Chicago, IL, USA
[c] University Hospital Zurich, Swiss HPB and Transplant Center, Zurich, Switzerland
[d] Department of Surgery, University of Sao Paolo, Sirio Libanes Hospital, Sao Paolo, Brazil
[e] AP-HP, Hôpital Paul Brousse, U Inserm 935, Univ Paris-Sud, Villejuif Cedex, Paris, France
[f] Royal Free Hospital, University College London, Department of HPB and Liver Transplant Surgery, London, UK
[g] Italian Hospital Buenos Aires, Department of Surgery, Division of HPB Surgery, Liver Transplant Unit, Buenos Aires, Argentina

ARTICLE INFO

*Article history:*
Accepted 22 February 2018
Available online xxx

ABSTRACT

*Objectives:* In the international associating liver partition and portal vein ligation for staged hepatectomy registry, more than 50% of patients underwent associating liver partition and portal vein ligation for staged hepatectomy with a right hepatectomy. This study evaluated the necessity of two-stage hepatectomies being performed as right hepatectomy associating liver partition and portal vein ligation for staged hepatectomy in patients with colorectal liver metastases versus right trisectionectomy associating liver partition and portal vein ligation for staged hepatectomy.

*Patients and Methods:* All patients registered between 2012 and 2017 undergoing associating liver partition and portal vein ligation for staged hepatectomy for colorectal liver metastases were included. A liver to body weight index of 0.5 or less prior to stage I in the presence of liver damage was used as an internationally accepted standard to justify a two-stage hepatectomy.

*Results:* Four-hundred and three patients with colorectal liver metastases with right hepatectomy associating liver partition and portal vein ligation for staged hepatectomy ($n = 183$) or right trisectionectomy associating liver partition and portal vein ligation for staged hepatectomy ($n = 220$) were analyzed. Presence of metastases in segments II/III, liver damage, number of patients on chemotherapy, and cycles were comparable, and there was a comparable response to chemotherapy. Liver to body weight index was different prior to stage 1 (right trisectionectomy associating liver partition and portal vein ligation for staged hepatectomy: 0.33 ± 0.12 versus right hepatectomy associating liver partition and portal vein ligation for staged hepatectomy: 0.40 ± 0,14; $P < .001$) and prior to stage 2 (right trisectionectomy associating liver partition and portal vein ligation for staged hepatectomy: 0.58 ± 0.17 versus right hepatectomy associating liver partition and portal vein ligation for staged hepatectomy: 0.66 ± 0,18; $P < .001$). Hypertrophy rates were similar between groups. As much as 16.9% and 7.2% of patients in right hepatectomy associating liver partition and portal vein ligation for staged hepatectomy and right trisectionectomy associating liver partition and portal vein ligation for staged hepatectomy had no apparent justification for a two-stage hepatectomy based on LBWI prior to stage 1 and absence of chemotherapy (<12 cycles).

* Corresponding author: Frankfurt University Hospital, Goethe-University Frankfurt/Main, Department of General and Visceral Surgery, Theodor-Stern-Kai 7, 60590 Frankfurt/Main, Germany.
*E-mail address:* andreas.schnitzbauer@kgu.de (A.A. Schnitzbauer).
[1] AAS and ES are both first authors

https://doi.org/10.1016/j.surg.2018.02.026


Please cite this article as: A.A. Schnitzbauer et al., Indicating ALPPS for Colorectal Liver Metastases: A Critical Analysis of Patients in the International ALPPS Registry, Surgery (2018), https://doi.org/10.1016/j.surg.2018.02.026

*Conclusion:* More than 15% of associating liver partition and portal vein ligation for staged hepatectomy procedures were performed in patients who may have had no indication for a two-stage hepatectomy, especially in the group of patients with right hepatectomy. Thus, it appears that there is a risk of the overuse of associating liver partition and portal vein ligation for staged hepatectomy because of its great potential to induce volume growth. Due to the high perioperative risk of associating liver partition and portal vein ligation for staged hepatectomy, indications should be carefully reconsidered.


## Introduction

ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) is a two-stage hepatectomy with an in-situ split of the liver parenchyma combined with a right portal vein ligation during stage 1 and the removal of the deportalized liver in stage 2. ALPPS was originally proposed as a surgical technique to enable two-stage, extended right hepatectomies and trisectionectomies in the setting of a small future liver remnant at risk for posthepatectomy liver failure.[1] Since then, the technique became popular despite early analyses demonstrating a posthepatectomy liver failure rate that was not better than one-stage extended hepatectomies with small future liver remnants.[2,3] Studies from the international ALPPS registry also identified a high number of patients (52%) undergoing ALPPS for right hepatectomies alone and not for more extended resections. Most patients had colorectal liver metastases (CLRM) with additional wedge resections of the future liver remnant. Proponents of ALPPS argued that small future liver volumes require a two-stage approach in these patients.[2] Parenchymal-sparing liver resections should be the standard of care in the surgical oncology of CRLM; however, the question arose if ALPPS was indicated in these patients, using volumetric criteria and considering the quality of hepatic parenchyma.[4] This study examined patients undergoing right hepatectomy ALPPS (rH-ALPPS) in the International ALPPS Registry and compared them with patients for whom ALPPS was originally developed, ie those undergoing right trisectionectomy ALPPS (rT-ALPPS).[5] We analyzed remnant volumes, kinetics of hypertrophy, the prevalence of abnormal liver histology, and the impact on morbidity and mortality. Our hypothesis was that some patients undergoing a right hepatectomy ALPPS may have been appropriate candidates for a one-stage hepatectomy given the generally accepted criteria of remnant size and liver quality.

## Patients and Methods

Access to the International ALPPS Registry was requested in early 2014, and final permission for the project was given on May 19, 2014. The database is registered at clinicaltrials.gov (NCT01924741) and has been approved by the ethics committee of the Canton of Zürich. Records from October 2012 to November 2017 were screened, and only patients undergoing ALPPS for CRLM were selected. Patients with missing information about the extent of resection and missing follow-up data were excluded. The analysis was restricted to patients with colorectal liver metastases, because volumetric indications for two-stage hepatectomies are well established for this indication. Demographics, concomitant disease, baseline volume of the functional liver remnant (FLR) and kinetic growth, complication rate according to Dindo-Clavien[6] and mortality were analyzed. The terminology right hepatectomy ALPPS and right trisectionectomy ALPPS was chosen.[7] Liver to body weight ratio (LBWR) of the FLR was evaluated. Patients with LBWI of $\geq$0.5 prior to stage 1 independent of the presence of liver damage were considered to be potentially resectable in one stage. Additionally, patients with a sFLR$\geq$0.3 in accordance with the definition by Vauthey et al and Shindoh et al[8,9] were evaluated and considered resectable independently from the grade of liver damage. Ninety-day overall-survival (90d-OS) and overall-survival (OS) were analyzed from the time of ALLPS stage 2 to last follow-up within 90 days after stage 2 or last contact to the patient, respectively. Patients lost to follow-up were censored at the day of last follow-up to a maximum of 90 days and last follow-up, respectively, after ALPPS stage 2. Data distribution was analyzed using the Kolmogorov-Smirnov test. T-test was used for normally distributed data. Categorical variables were tested with chi-square test. Survival analyses were performed using the Kaplan-Meier survival and COX regression method. Statistical analysis was performed with SPSS Statistics (IBM SPSS Software Package 25, Ehningen, Germany).

## Results

### *Patient selection*

From October 2012 to November 2017, 1,041 patients were registered in the ALPPS registry; 521 cases involved CRLM of whom 442 patients (85%) were documented with at least 3 months of follow-up at that cut-off date. Among the 442 patients with available data, 403 (91%) underwent ALPPS as either a right hepatectomy (rH) or right trisectionectomy (rT). The final analysis was carried out on these 403 patients with CRLM. Of thoese, 220 patients underwent rT-ALPPS and 183 underwent rH-ALPPS (Fig. 1).

### *Patient demographics*

Table 1 shows the demographics of the two cohorts. No differences between cohorts were found.

### *Tumor-specific characteristics*

Table 2 shows the tumor-specific characteristics. Synchronous metastases (present at the time-point of primary diagnosis) were

**Table 1**
Descriptive data and prevalence of concomitant disease.

| | Right trisectionectomy ALPPS $n=220$ | | Right hepatectomy ALPPS $n=183$ | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | *P*-value |
| Age (years) | 59.1 | 10.7 | 58.7 | 11.8 | .684 |
| BMI | 25.8 | 3.9 | 25.8 | 4.2 | .990 |
| BSA ($m^2$) | 1.87 | 0.31 | 1.87 | 0.26 | .993 |
| SLV (mL) | 1589 | 363 | 1590 | 285 | .953 |
| Sex (F/M) | 78/141 | | 63/118 | | .748 |
| Race | Black: 3<br>Caucasian: 212<br>Oriental: 2<br>Other: 3 | | Black: 1<br>Caucasian: 166<br>Oriental: 7<br>Other: 8 | | .053 |

Groups compared were right trisectionectomy ALPPS and right hepatectomy ALPPS for colorectal liver metastases. Data are given as mean with standard deviation (SD). BMI: body mass index; BSA: body surface area; SLV: standardized liver volume. Equal distribution was tested by Kolmogorov-Smirnov-test, differences between groups were tested by *t*-test. Categorical variables were tested by chi-square test.

Please cite this article as: A.A. Schnitzbauer et al., Indicating ALPPS for Colorectal Liver Metastases: A Critical Analysis of Patients in the International ALPPS Registry, Surgery (2018), https://doi.org/10.1016/j.surg.2018.02.026

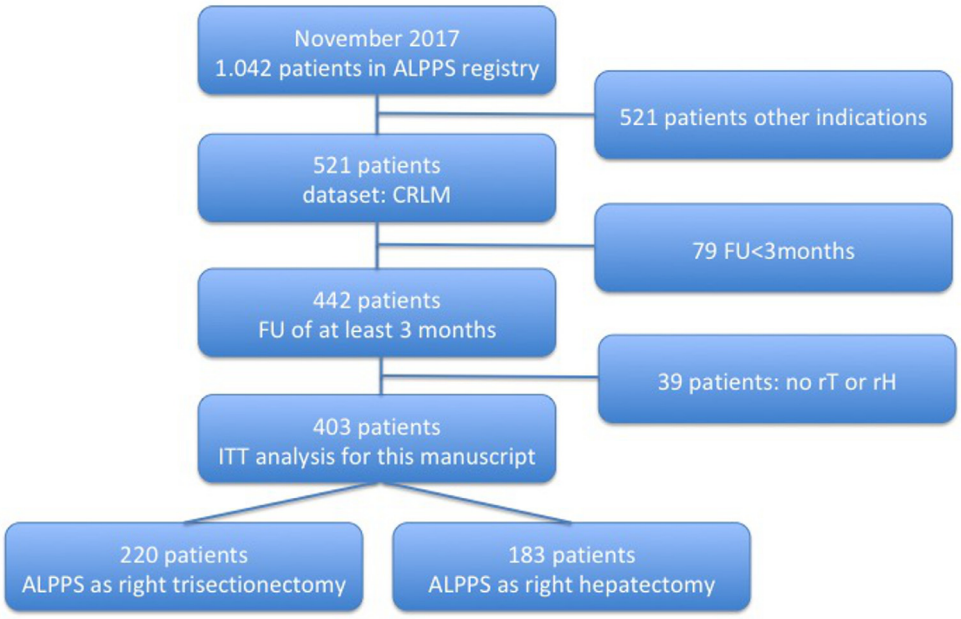


**Fig. 1.** Flow chart of patients excluded from analysis based on missing data and diagnosis other than CRLM. FU: follow-up; ITT: intention to treat.

**Table 2**
Tumor characteristics of right trisectionectomy ALPPS and right hepatectomy ALPPS for colorectal liver metastases.

| | | Right trisectionectomy ALPPS $n = 220$ | | Right hepatectomy ALPPS $n = 183$ | | P-value |
|---|---|---|---|---|---|---|
| Occurrence of metastases | | Synchronous: 170<br>Metachronous: 38<br>N.A.: 12 | | Synchronous: 132<br>Metachronous: 46<br>N.A.: 5 | | .075 |
| Patients with metastases in segments II or III (n) | | 126 | | 144 | | .306 |
| Volume of lesions in segments II and III (mL) | | 44 ± 132 | | 38 ± 64 | | .409 |
| Maximum size of largest tumor (mm ± SD) | | Prior CTx<br>63.1 ± 42.1 | Post CTx<br>45.1 ± 30.1 | Prior CTx<br>50.7 ± 28.9 | Post CTx<br>43.9 ± 23.7 | .08 (prior CTx)<br>.460 (post CTx) |
| CTx number of cycles (n ± SD) | | 8.6±8.6 | | 8.9±9.2 | | .767 |
| Number of patients on CTx prior to ALPPS | | 168 | | 136 | | .644 |
| Chemo-therapy-associated liver damage (y/n) | Steato-hepatitis | 20/146 | | 13/100 | | .890 |
| $n = 174$ rT ALPPS | Fibrosis | 28/130 | | 25/85 | | .375 |
| $n = 122$ rH ALPPS | Cash | 61/103 | | 41/69 | | .990 |
| | SOS | 30/125 | | 30/77 | | .100 |
| | Macrosteatosis | 43/104 | | 20/80 | | .102 |

Data are given in mean and standard deviation (SD). Data for chemotherapy-associated liver damage were available for 77 in the right trisectionectomy ALPPS and for 50 in the right hepatectomy ALPPS respectively. CTx: chemotherapy; n.a.: not applicable; CASH: chemotherapy-associated steatohepatitis, SOS: sinusoidal obstruction syndrome. Equal distribution was tested by Kolmogorov-Smirnov test, differences between groups were tested by *t*-test. Categorical variables were tested by chi-square test.

the most common presentation, while metachronous metastases (occurring >6 months after primary diagnosis) were less common. The time of occurrence of metastases was not documented in 12 patients in the rT-ALPPS and 5 in the rH-ALPPS. There was no difference in the number of patients with CRLMs or the estimated volume of tumor in segments II and III prior to stage 1 (rT-ALPPS: $n = 126$ versus rH-ALPPS: $n = 144$; $P = .306$). In the rH-ALPPS group, 26% of patients did not receive chemotherapy prior to ALPPS compared to 24% of patients in the rT-ALPPS group (Table 2).

*Liver histology*

The incidence of steatohepatitis, fibrosis, sinusoidal obstruction syndrome (SOS), macrosteatosis, and chemotherapy-associated steatohepatitis (CASH) in rT-ALPPS and rH-ALPPS are shown in Table 2. Data were complete and available in 174 patients in rT-ALPPS and 122 patients in rH-ALPPS (73.4%). Data were not different between the groups.

*Volume and growth*

Table 3 shows that all volume parameters point toward larger remnant liver volumes in the rH-ALPPS group. Prior to stage 1, the FLR estimated by mL, LBWI in percent[10] and standardized FLR (sFLR) (Vauthey formula) in percent[11,12] were greater in the rH-ALPPS ($P < .001$). There was no difference in the number of patients with tumor burden (number and total volume of the metastases) in segments II and III (Table 3) between groups. Moreover, and more importantly, the weight of liver tissue in segments II and III removed for the metastasectomies did not differ between the groups. Also, after the period of hypertrophy and prior to stage 2, remnant volumes were greater in the rH-ALPPS group. The relative growth of the FLR expressed as % hypertrophy was similar in both groups (rT-ALPPS: 81% versus rH-ALPPS: 77%; $P = .390$). As far as the indications for regenerative liver surgery are concerned, 22/220 patients (10.0%) undergoing rT-ALPPS and 37/183 patients (20.2%) undergoing rH-ALPPS had a LBWI of 0.5 or greater prior to stage 1 ($P = .005$). Choosing the standards suggested by the MD Anderson

**Table 3**
Volumetric and intraoperative characteristics.

| | | Right trisectionectomy ALPPS $n=220$ | | Right hepatectomy ALPPS $n=183$ | | |
|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | P-value |
| Prior Stage 1 | TLV clean (mL) | 1072 | 600 | 1223 | 570 | .014 |
| | Volume FLR (mL) | 359 | 147 | 422 | 149 | < .001 |
| | Volume FLR clean (mL) | 334 | 119 | 398 | 144 | < .001 |
| | Remnant LBWI | 0.33 | 0.12 | 0.40 | 0.14 | < .001 |
| | sFLR (Vauthey) | 0.20 | 0.09 | 0.24 | 0.10 | < .001 |
| | Patients LBWI ≥0.5 (*n*) | 22 (10.0%) | | 37 (20.2%) | | .005 |
| | Patients sFLR ≥0.3 (*n*) | 24 (10.9%) | | 51 (27.8%) | | < .001 |
| | Patients with and without liver damage and LBWI ≥0.5 | 13/6 | | 14/8 | | .367 |
| | Patients with and without liver damage and sFLR (Vauthey) ≥0.3 | 10/7 | | 17/15 | | .285 |
| | Patients LBWI ≥0.5 with more than 12 cycles of chemotherapy | 6 (2.7%) | | 6 (3.3 %) | | .746 |
| | Patients sFLR ≥0.3 (*n*) with more than 12 cycles of chemotherapy | 3 (1.4%) | | 8 (4.3%) | | .074 |
| | Incision-suture time (min) | 322 | 123 | 300 | 105 | .08 |
| | CVP (cmH2O) | 6.7 | 10.6 | 5.8 | 6.9 | .460 |
| | Pringle (yes) | 126 | | 112 | | .843 |
| | Pringle total (min) | 16 | 21 | 17 | 23 | .837 |
| | Weight wedge seg II (g) | 34 ± 40 | | 33 ± 38 | | .862 |
| | Weight wedge seg III (g) | 28 ± 43 | | 40 ± 68 | | .07 |
| | Hanging maneuver (yes) | 102 | | 78 | | .026 |
| | Anterior approach (yes) | 88 | | 52 | | .007 |
| | Lymphadenectomy (yes) | 52 | | 32 | | .185 |
| ALPPS modifications | classic | 196 | | 154 | | .112 |
| | partial | 12 | | 14 | | |
| | hyprid | 4 | | 3 | | |
| | tourinquet | 8 | | 12 | | |
| Time between stages (d) | | 16.9 | 29.5 | 22.5 | 50.5 | .008 |
| Prior Stage 2 | TLV clean (mL) | 1227 | 609 | 1422 | 583 | .02 |
| | Volume FLR clean (mL) | 578 | 1745 | 663 | 182 | < .001 |
| | Remnant LBWI (Truant) | 0.58 | 0.17 | 0.66 | 0.18 | < .001 |
| | sFLR (Vauthey) | 0.34 | 0.15 | 0.39 | 0.15 | < .001 |
| | Growth of FLR (%) | 81 | 50 | 77 | 49 | .390 |
| | Incision-suture time (min) | 172 | 86 | 152 | 73 | .023 |

Groups compared were right extended hepatectomies and right hepatectomies undergoing ALPPS for colorectal liver metastases. Data are given in mean and standard deviation (SD). TLV: total liver volume; FLR: future liver remnant; LBWI: remnant liver to body weight ratio: FLR volume divided by body weight (BW); sFLR: standardized future liver remnant according to Vauthey; CVP: central venous pressure; atyp.: atypical. Information on classic ALPPS versus modified techniques of ALPPS were not equal distribution was tested by Kolmogorov-Smirnov test, differences between groups were tested by *t*-test. Notably, as expected there was no equal distribution between groups.

Cancer Center of a standardized FLR >0.3, the sFLR showed that 27.8% of patients in the rH-ALPPS group underwent ALPPS with an sFLR >30% compared to only 10.9% in rT-ALPPS group ($P < .001$). It was determined that in 6 of the 37 patients undergoing rH-ALPPS beyond the LBWI criteria of 0.5, ALPPS was justified by more than 12 cycles of preoperative chemotherapy. The same applied for 6 of 51 patients undergoing rH-ALPPS beyond the sFLR criteria of 0.3. The number of patients with liver damage exceeding the thresholds of 0.5 and 0.3 in FLR were low and cannot only explain the rationale for the indication of the need for an ALPPS in these patients in approximately 30% of patients.

*Morbidity and survival*

Table 4 shows that 90-day mortality after stage 2 was 8.6% for rT-ALPPS, and 6.5% for rH-ALPPS. Complications after stage I and II were equally distributed between the two groups, but however, there was a trend ($P > .05$ but less than .1) towards more complications in the rT group as expected. Specifically the rate of posthepatectomy liver failure (ISGLS) after stage 2 was greater in rT-ALPPS patients. In Fig. 2 the Kaplan-Meier curve of OS suggests that the median survival was not different between the two groups (30.1 ± 12.3 vs. 31.7 ± 11.8 months $P=.064$). Survival was dependent on the growth of the FLR as Figs. 3 and 4 show; patients who had a FLR ≥0.5 (Remnant LBWI [Truant] before stage 1 and 2) (FLRhi) versus FLR <0.5 before stage 1 and ≥0.5 before stage 2 (FLRlohi) versus FLRs <0.5 before stage 1 and 2 showed significantly worse outcome for patients who did not show sufficient interstage volume growth (FLRhi: 24.6 ± 9.2, FLRlohi: 32.4 ± 12.1 and FLRlo: 29.8 ± 12.2; $P=.03$). The same was detected when data were grouped in the same way for the sFLR (Vauthey) using the threshold of 0.3: Mean survival was and FLRhi: 27.3 ± 10.6, FLRlohi: 33.5 ± 17.0 and FLRhi: 25.1 ± 14.0; $P=.012$.

## Discussion

This study comparing rH-ALPPS and rT-ALPPS for CRLMs in the largest registry for ALPPS patients shows that up to one third of patients undergo ALPPS without the generally accepted need for a two-stage hepatectomy. Using an LBWI of 0.5 as a cut-off to seriously consider regenerative liver surgery was first proposed by Truant et al[10] and later used by Schnitzbauer et al[1] in the initial description of the in-situ split technique to explain why patients in 5 German centers required an effective strategy to be converted to resectability. ALPPS may have developed into a popular technique in situations of perceived unresectabilty, which may not always be justifiable by objective data. Based on this analysis of a voluntary, yet fairly comprehensive international ALPPS registry, a number of

**Table 4**
Morbidity and mortality in patients undergoing rT-ALPPS and rH-ALPPS.

| Morbidity and Mortality | | Right trisectionectomy ALPPS $n = 220$ | Right hepatectomy ALPPS $n = 183$ | P-value |
|---|---|---|---|---|
| Dindo-Clavien (after stage 1) | 0 | 165 | 128 | .052 |
| | I | 13 | 7 | |
| | II | 25 | 21 | |
| | IIIa | 10 | 5 | |
| | IIIb | 4 | 13 | |
| | IVa | 1 | 4 | |
| | IVb | 2 | 3 | |
| Dindo-Clavien (after stage 2) | 0 | 92 | 89 | .065 |
| | I | 48 | 27 | |
| | II | 16 | 9 | |
| | IIIa | 25 | 25 | |
| | IIIb | 16 | 18 | |
| | IVa | 6 | 4 | |
| | IVb | 0 | 4 | |
| | V (90 days) | 19 | 10 | |
| Complication category (after stage 1) | Biliary | 14 | 10 | .685 |
| | Hemorrhage | 1 | 3 | |
| | Liver failure (ISGLS) | 16 | 8 | |
| Complication category (after stage 2) | Biliary | 31 | 20 | < .001 |
| | Hemorrhage | 2 | 7 | |
| | Liver failure (ISGLS) | 41 | 22 | |

Data were analyzed using chi-square test. *P*-values < .5 were regarded as statistically significant. ISGLS–International Study Group of Liver Surgery .[23]

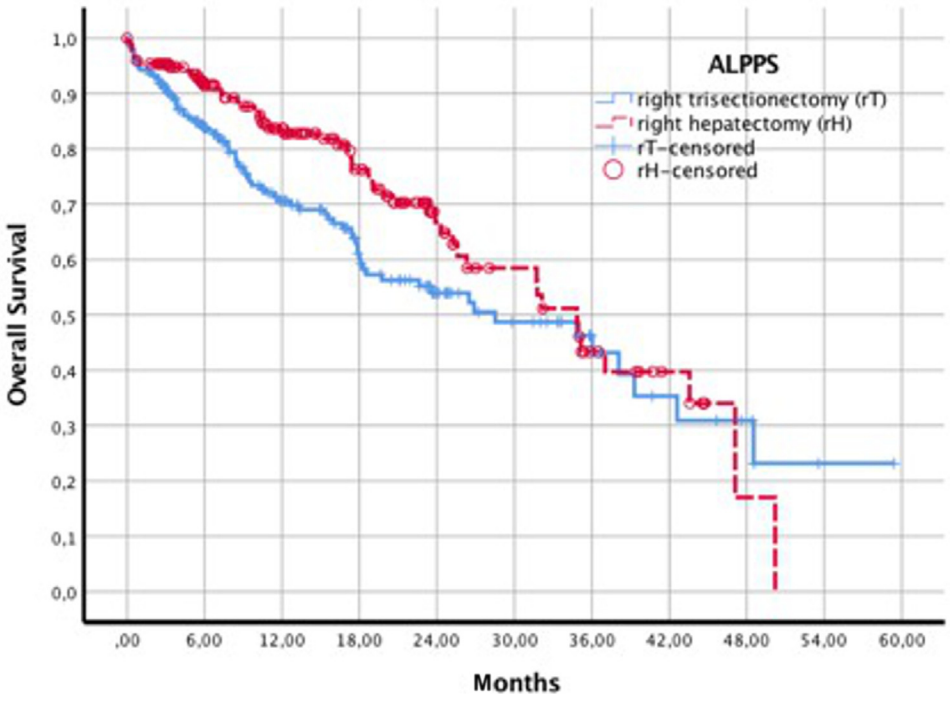


**Fig. 2.** Kaplan-Meier curve of overall survival of patients with CRLM undergoing right trisectionectomies (rT) versus right hepatectomies (rH). Mean survival was 30.1 ± 12.3 versus 31.7 ± 11.8 months $P = 0.064$.

patients with rH-ALPPS may very well have been resectable with a one-stage hepatectomy, thereby avoiding the additional risks of an ALPPS. Not surprisingly, these patients also had a better outcome, because there may have been no need for volume and functional enhancement in many of these patients.

In general, one would expect that patients undergoing rH-ALPPS would have more metastasectomies or removal of a greater volume of liver parenchyma in the FLR during stage 1 to justify a two-stage approach. Resections in segments 2 and 3 would decrease the FLR and thus justify the need for a regenerative liver operation before a right hepatectomy to preserve liver function after stage 2. This expectation however, did not appear to be the case in the patients examined. There were no differences in the number and volume of tumors resected in the FLR. Our other hypothesis was that patients undergoing rH-ALPPS would have less total liver volume, which was not the case either.

Next, our hypothesis was that patients undergoing ALPPS with an LBWI of 0.5 and greater would have compromised parenchymal liver quality by having undergone more cycles of preoperative chemotherapy as the underlying rationale to perform ALPPS despite FLR volumes LBWI >0.5 prior to resection. This expectation was the case in only 16% of the patients undergoing

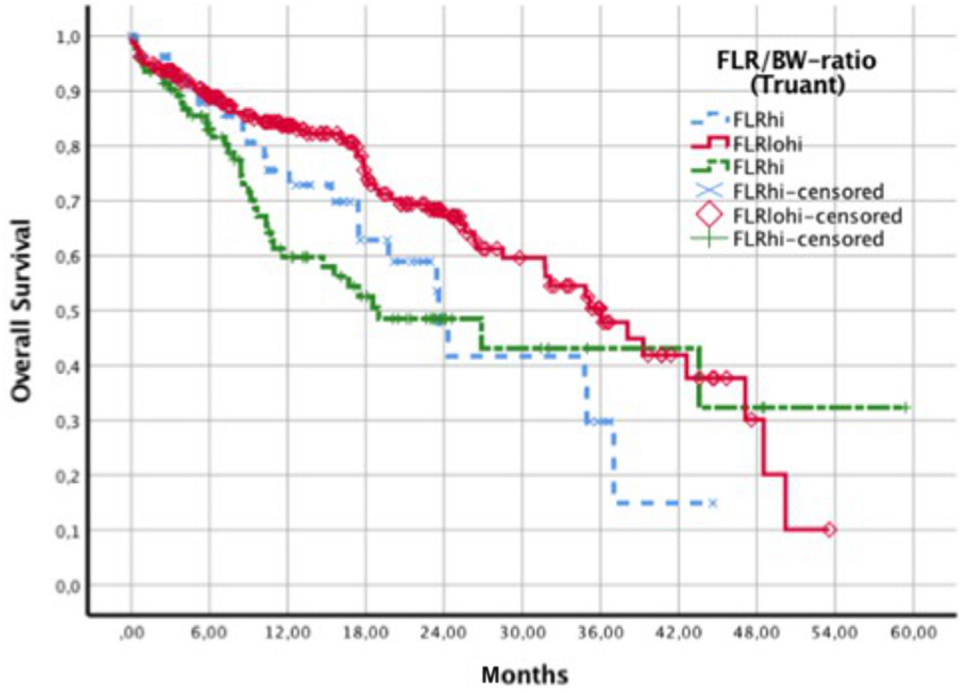


**Fig. 3.** Kaplan-Meier overall survival curves of patients with FLRs ≥0.5 (Remnant LBWI [Truant] before stage 1 and 2) (FLRhi) versus FLRs <0.5 before stage 1 and ≥0.5 before stage 2 (FLRlohi) versus FLRs <0.5 before stage 1 and 2. Mean survival was FLRhi: 24.6 ± 9.2, FLRlohi: 32.4 ± 12.1 and FLRlo: 29.8 ± 12.2; $P = .03$.

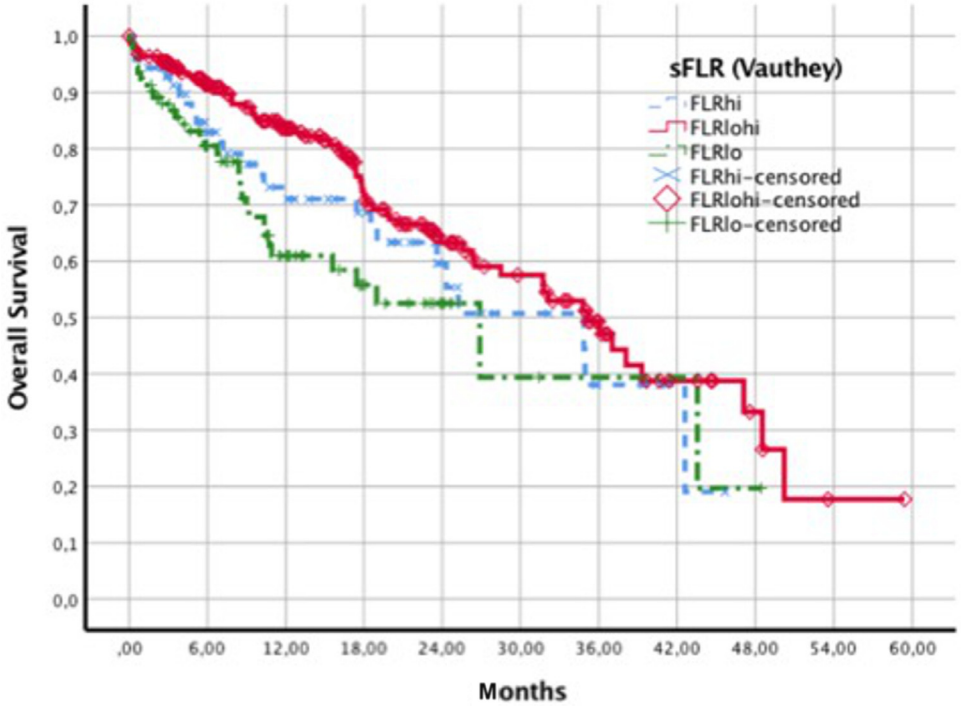


**Fig. 4.** Kaplan-Meier curves of overall survival in patients with FLRs ≥ 0.5 (sFLR (Vauthey) before stage 1 and 2) (FLRhi) versus FLRs <0.3 before stage 1 and ≥0.3 before stage 2 (FLRlohi) versus FLRs <0.3 before stage 1 and 2. Mean survival was and FLRhi: 27.3 ± 10.6, FLRlohi: 33.5 ± 17.0 and FLRhi: 25.1 ± 14.0; $P = .012$.

rH-ALPPS for the LBWI of 0.5 criteria as well as for the MD Anderson sFLR >0.3 criteria. These findings support the conclusion that the surgeons performing a rT-ALPPS on multiple patients in the registry may have believed that a two-stage hepatectomy was necessary based on perceived rather than objective criteria of non-resectability. Given that ALPPS has been criticized for high morbidity and mortality and given that past analyses of the registry tried to single out the appropriate indications with acceptable morbidity and mortality,[2,3,13-15] the finding that ALPPS is performed in patients who may not have needed this regenerative liver surgery, may help to prevent unnecessary ALPPS procedures in the future.

Despite an "acceptable" number of cycles of preoperative chemotherapy, the liver histology may have been compromised in some of the patients undergoing ALPPS outside the accepted standard volume indications; however, when the histology data available for these cohorts were analyzed, it does not appear that

Please cite this article as: A.A. Schnitzbauer et al., Indicating ALPPS for Colorectal Liver Metastases: A Critical Analysis of Patients in the International ALPPS Registry, Surgery (2018), https://doi.org/10.1016/j.surg.2018.02.026

SOS and CASH were present at a greater rate than described in the literature. Rubbia-Brandt et al described moderate to severe SOS in up to 54% of patients, whereas the prevalence of CASH during modern chemotherapy ranges from 15% to 47% as described in a comprehensive review by Chun et al.[16,17] Morbidity and 90-day mortality is increased when patients undergo major hepatic resections after chemotherapy-induced steatosis or sinusoidal injury,[18,19] but this alone, however, does not explain the use of ALPPS in patients with LBWI >0.5.

It is important to note that the majority of patients undergoing rH-ALPPS had a starting sFLR according to Vauthey of greater than 0.25, while some literature supports the possibility of safe liver resections for CRLMs in patients with an sFLR >0.25 who have undergone prior chemotherapy.[8] Using an even more conservative cutoff of 0.3 and greater, up to one third of patients in the rH-ALPPS group may have been resectable in one stage. The low rate of liver failure in the rH-ALPPS patients compared to the rT-ALPPS patients may be explained by the liberal volumetric indications in this group rather than being a virtue of ALPPS per se. The important and controversial question behind this analysis is whether rH-ALPPS is a rational option in the menu of options presented by regenerative liver surgery for the majority of patients in 2017. Beyond the suspicion that no regenerative maneuver was necessary in some of these patients, there also remains the option of portal vein embolization (PVE) with a two-stage hepatectomy, besides other well established approaches with interstage chemotherapy or interventional techniques, also without PVE. The hypertrophy achieved in rT and rH was similar. Up to 50% hypertrophy may be achievable by PVE with embolization of segment 4 as has been demonstrated by experienced centers,[12,20] and therefore, the question has to be asked about the rationale for ALPPS in patients with enough remnant volume, as in our study of patients undergoing an rH-ALPPS. The unavailability of PVE or the lack of confidence in the ability of the local interventional radiologists to perform a satisfactory PVE could also in theory be the reason to perform an rH-ALLPS. Randomized data from prospective trials are now available from the LIGRO-trial[21] and show that ALPPS is more effective than PVE in inducing hypertrophy of the FLR, resulting in similar short-term morbidity.

There are a number of important limitations to this study. First, there is substantial selection bias in a voluntary registry without independent monitoring. There may be a selection bias to include patients based on outcomes rather than including them in sequential and complete order. The aim of our study was to determine if the indications for an rH-ALLPS in the ALPPS registry is always indicated based on objective measurements of the FLR and/or the presence (either measured or assumed) of liver parenchymal damage related to prior chemotherapy of underlying liver disease.

Notably, 50% of patients undergoing ALPPS for CRLM receive rH-ALPPS, yielding an equal distribution of the two techniques in the registry. Liver damage was also distributed equally between the groups with complete data for over 70% of patients. This rules out relevant selection with regards to these two specific and central parameters of the study. Despite the flow diagram (Fig. 1) showing the necessary censoring due to incomplete data, this registry with all its deficiencies still remains a good indicator of current practice. Further, factors playing a role in the thinking process of surgeons who selected a regenerative liver surgery may not be captured by the data collection of the registry. Of course, when tumor load in the left liver is considered to be an indication for ALPPS, it would have been better to have imaging data, because the localization of lesions may have given a better understanding of why surgeons felt it was necessary to perform ALPPS rather than just based on the number of lesions. Unfortunately, imaging data are not part of the ALLPS registry. In any case, the extent of parenchymal resection in the left lobe to deal with the CRLMs there is not considered in the calculation of volume of the FLR and therefore, we did not further pursue such concerns, because the resected liver tissue showed the same weight between the groups and was similar to the volume calculated prior to stage 1. The same concern is evident for histology, where data are not only incompletely entered, but in many cases may not have been known prior to performing the procedures. Some of the histology data entered may have been entered only after the pathology reports returned. Ultimately, the decision about whether a regenerative liver surgery like ALLPS is necessary should depend on a test of regional liver function within the FLR. Unfortunately, in the International ALPPS registry there is only scattered information about liver function of the FLR with many different methodologies. HIDA, the most hopeful of the current regional liver function tests, is not standardized across centers. Reliable information about liver function in the liver remnant can only be provided by close collaboration with standardized testing in a reference center, as demonstrated recently by a collaborative group of authors of this study.[22]

In conclusion, this analysis shows that in this voluntary registry of ALLPS procedures, up to one third of ALPPS procedures for CRLM may well be performed without an objective indication to perform a two-stage hepatectomy rather than a one-stage right hepatectomy. Not surprisingly, surgical outcomes were relatively good in this patient population. Despite these results of good outcomes after the rH-ALLPS, indications for ALPPS should continue to be vetted critically by multidisciplinary tumor boards based on accepted criteria of RLV, number of prior cycles of chemotherapy, and histologic criteria of the presence or absence of underlying parenchymal hepatic damage based on at the least a fresh frozen section during stage 1, when ALPPS is considered.

## References

1. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann Surg*. 2012;255:405–414.
2. Schadde E, Ardiles V, Robles-Campos R, et al. Early survival and safety of ALPPS: first report of the International ALPPS Registry. *Ann Surg*. 2014;260(829):836–838.
3. Schadde E, Raptis DA, Schnitzbauer AA, et al. Prediction of mortality after ALPPS Stage-1: an analysis of 320 patients from the International ALPPS Registry. *Ann Surg*. 2015;262:780–786.
4. Mise Y, Aloia TA, Brudvik KW, et al. Parenchymal-sparing hepatectomy in colorectal liver metastasis improves salvageability and survival. *Ann Surg*. 2016;263:146–152.
5. Belgihiti J, Clavien PA, Gadzijev E, et al. The Brisbane 2000 terminology of liver anatomy and resections. *Hpb*. 2000;2:333–339.
6. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
7. Linecker M, Kron P, Lang H, et al. Too many languages in the ALPPS: preventinganother tower of Babel? *Ann Surg*. 2016 Epub ahead of print January 13.
8. Shindoh J, Tzeng C-WD, Aloia TA, et al. Optimal future liver remnant in patients treated with extensive preoperative chemotherapy for colorectal liver metastases. *Ann Surg Oncol*. 2013;20:2493–2500.
9. Vauthey JN, Chaoui A, Do KA, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery*. 2000;127:512–519.
10. Truant S, Oberlin O, Sergent G, et al. Remnant liver volume to body weight ratio >or = 0.5%: A new cut-off to estimate postoperative risks after extended resection in noncirrhotic liver. *J Am Coll Surg*. 2007;204:22–33.
11. Vauthey J-N, Abdalla EK, Doherty DA, et al. Body surface area and body weight predict total liver volume in Western adults. *Liver Transpl*. 2002;8:233–240.
12. Kishi Y, Abdalla EK, Chun YS, et al. Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. *Ann Surg*. 2009;250:540–548.
13. Schadde E, Schnitzbauer AA, Tschuor C, et al. Systematic review and meta-analysis of feasibility, safety, and efficacy of a novel procedure: associating liver partition and portal vein ligation for staged hepatectomy. *Ann Surg Oncol*. 2014 Epub ahead of print December 2.
14. D'Haese JG, Neumann J, Weniger M, et al. Should ALPPS be used for liver resection inintermediate-stage HCC? *Ann Surg Oncol*. 2015 Epub ahead of print December 8.

Please cite this article as: A.A. Schnitzbauer et al., Indicating ALPPS for Colorectal Liver Metastases: A Critical Analysis of Patients in the International ALPPS Registry, Surgery (2018), https://doi.org/10.1016/j.surg.2018.02.026

15. Li J, Girotti P, Königsrainer I, et al. ALPPS in right trisectionectomy: a safe procedure to avoid postoperative liver failure? *J Gastrointest Surg*. 2013;17:956–961.
16. Rubbia-Brandt L, Lauwers GY, Wang H, et al. Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. *Histopathology*. 2010;56:430–439.
17. Chun YS, Laurent A, Maru D, et al. Management of chemotherapy-associated hepatotoxicity in colorectal liver metastases. *Lancet Oncol*. 2009;10:278–286.
18. Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg*. 2006;243:1–7.
19. Vauthey J-N, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol*. 2006;24:2065–2072.
20. Shindoh J, Tzeng C-WD, Aloia TA, et al. Portal vein embolization improves rate of resection of extensive colorectal liver metastases without worsening survival. *Br J Surg*. 2013;100:1777–1783.
21. Sandström P, Røsok BI, Sparrelid E, et al. ALPPS improves resectability compared with conventional two-stage hepatectomy in patients with advanced colorectal liver metastasis: results from a Scandinavian multicenter randomized controlled trial (LIGRO Trial). *Ann Surg*. 2017 Epub ahead of print September 11.
22. Olthof PB, Tomassini F, Huespe PE, et al. Hepatobiliary scintigraphy to evaluate liver function in associating liver partition and portal vein ligation for staged hepatectomy: liver volume overestimates liver function. *Surgery*. 2017;162:775–783.
23. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*. 2011;149:713–724.

Please cite this article as: A.A. Schnitzbauer et al., Indicating ALPPS for Colorectal Liver Metastases: A Critical Analysis of Patients in the International ALPPS Registry, Surgery (2018), https://doi.org/10.1016/j.surg.2018.02.026