

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)

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Objective: The aim of the study was to evaluate if associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) could increase resection rates (RRs) compared with two-stage hepatectomy (TSH) in a randomized controlled trial (RCT).

Background: Radical liver metastasis resection offers the only chance of a cure for patients with metastatic colorectal cancer. Patients with colorectal liver metastasis (CRLM) and an insufficient future liver remnant (FLR) volume are traditionally treated with chemotherapy with portal vein embolization or ligation followed by hepatectomy (TSH). This treatment sometimes fails due to insufficient liver growth or tumor progression.

Methods: A prospective, multicenter RCT was conducted between June 2014 and August 2016. It included 97 patients with CRLM and a standardized FLR (sFLR) of less than 30%. Primary outcome—RRs were measured as the percentages of patients completing both stages of the treatment. Secondary outcomes were complications, radicality, and 90-day mortality measured from the final intervention.

Results: Baseline characteristics, besides body mass index, did not differ between the groups. The RR was 92% [95% confidence interval (CI) 84%–100%] (44/48) in the ALPPS arm compared with 57% (95% CI 43%–72%) (28/49) in the TSH arm [rate ratio 8.25 (95% CI 2.6–26.6); $P < 0.0001$]. No differences in complications (Clavien–Dindo $\geq 3a$) [43% (19/44) vs 43% (12/28)] [1.01 (95% CI 0.4–2.6); $P = 0.99$], 90-day mortality [8.3% (4/48) vs 6.1% (3/49)] [1.39 [95% CI 0.3–6.6]; $P = 0.68$] or R0 RRs [77% (34/44) vs 57% (16/28)] [2.55 [95% CI 0.9–7.1]; $P = 0.11$] were observed. Of the

patients in the TSH arm that failed to reach an sFLR of 30%, 12 were successfully treated with ALPPS.

Conclusion: ALPPS is superior to TSH in terms of RR, with comparable surgical margins, complications, and short-term mortality.

Keywords: associating liver partition and portal vein ligation for staged hepatectomy, colorectal liver metastasis, portal embolization, portal ligation, RCT, two-stage hepatectomy

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A denocarcinoma of the colon/rectum is the third most common malignancy in the world,¹ affecting more than 1.3 million patients annually. Of these patients, 30% to 50% present with liver metastasis at the time of diagnosis or develop metastasis later.² Surgery is the primary curative treatment option for patients with colorectal liver metastases (CRLMs),² and surgical treatment results in a 5-year survival rate of close to 50%.² With improvements in perioperative chemotherapy, surgical techniques, and methods of anesthesia, resection is possible in an increasing number of patients with more advanced diseases.

Patients with bilateral CRLM and a small estimated tumor-free future liver remnant (FLR) present a treatment challenge. These patients may need a two-stage hepatectomy (TSH) in which portal venous ligation (PVL) or portal venous embolization (PVE) is included in the first stage to stimulate hypertrophy of the FLR before final resection.³ This approach generates a 27% to 39% increase in FLR volume in 4 to 8 weeks, although longer periods may be needed.⁴ The risks inherent in this method are tumor progression during the waiting period and insufficient hypertrophy, making resection impossible in 25% to 38% of the patients preparing to undergo TSH.^{5–8}

A new concept of liver resection, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), was described in 2011.⁹ The first clinical series of ALPPS was conducted in 2012.¹⁰ This method seems to increase liver growth rate and volume, which renders more patients resectable in a shorter amount of time. However, in the initial study 68% of the patients experienced complications and the surgical mortality rate was 12%. Since the first description of ALPPS, there has been a great deal of interest in this treatment. However, criticism of the approach has been raised mainly regarding surgical morbidity and mortality.¹¹

The international ALPPS registry (www.ALPPS.org) was initiated, and the first report from the registry included 202 patients.¹² Feasibility was found to be 98%, and Clavien–Dindo complications $\geq 3a$ were observed in 36% of patients with CRLM.¹³

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The 90-day mortality rate was 8% for the patients with CRLM who underwent ALPPS, which is comparable to that of CRLM patients who underwent TSH.^{11,12} This analysis and other published results also indicate rapid and increased hypertrophy of the FLR with ALPPS compared with the effects of TSH.^{11,14} If ALPPS may have a role in treatment of patients with advanced CRLM, a larger proportion of patients must reach tumor freedom in the liver without an increased frequency of severe complication or perioperative mortality. Given the reported safety profile of ALPPS in treating CRLM, this method should be compared with traditional TSH in a randomized setting with resection rates (RRs) as primary endpoint.

HYPOTHESIS

A higher proportion of patients can be resected with ALPPS than with traditional TSH. In addition, this can be achieved without higher complication rates, increased perioperative mortality, or reduced radical resections.

METHODS

Study Design

The LIGRO Trial (NCT02215577) was a multicenter, randomized, controlled trial involving 1 Danish, 1 Norwegian, and 4 Swedish university hospitals. The ethics committees in each country accepted the trial. Written informed consent was obtained from each patient enrolled in the study. An independent safety board provided trial oversight after every 20 patients included. If significant differences in severe morbidity or mortality were observed, the study would be discontinued.

A total of 10 liver surgeons participated in the trial, all with extensive experience of complex liver surgery. All centers had performed at least 2 ALPPS procedures before the start of the trial. The technical aspects were discussed in detail before the start of the trial. All authors were responsible for every element of the trial, including its design, data collection, data analysis, and data interpretation. All data were collected by the site investigators and trial staff at each participating site and then transferred to the data-coordinating center for analysis. All data remained confidential during the trial. All authors were involved in every step of writing the manuscript. All authors confirm the accuracy and completeness of the data and vouch for the fidelity of the trial to the protocol.

Previous comparison between the ALPPS procedure and traditional TSH in a randomized setting has not been performed. We therefore found it of importance in this first stage to evaluate RRs between the 2 methods, and to see if the ALPPS was superior in this regard without causing more severe complications or increasing perioperative mortality. From a patient's standpoint, the ultimate goal is tumor freedom and long-term survival, and this also needs to be evaluated before the role of the ALPPS procedure can be decided.

TRIAL POPULATION

The institutions participating in the trial serve a total catchment population of approximately 15 million inhabitants. Between June 2014 and August 2016, 100 patients who fulfilled the inclusion criteria were identified (Table 1). These 100 patients were randomly assigned to the TSH group (50 patients) or the ALPPS group (50 patients). During the trial period, a total of 1672 (140–519 at each center) patients with CRLM underwent operations at the trial centers. A CONSORT flowchart of the trial progress is shown in Figure 1.

DISEASE STAGING

Before inclusion in the study, patients received chemotherapy and were examined by multidisciplinary tumor boards that included

TABLE 1. Inclusion and Exclusion Criteria*

Inclusion:

1. Patients with colorectal liver metastasis requiring liver resection, not resectable in one step because of a future liver remnant/standardized total liver volume ratio of <30%, without any minimal volume limit
2. All patients should have been treated with preoperative chemotherapy with at least stable disease and been evaluated and accepted for inclusion at one of the centers multidisciplinary boards.
3. Extrahepatic metastatic disease or unresected primary tumors are not exclusion criteria if they can be addressed surgically in the future.

Exclusion:

1. Progressive disease on preoperative chemotherapy
2. Cirrhosis
3. Significant comorbidity rendering subjects unsuitable for major surgery
4. Age <18 yrs

*Information regarding all exclusion and inclusion factors was available at the multidisciplinary conference making very few patients excluded in the outpatients clinic at randomization.

radiologists, oncologists, and liver surgeons. Patients with resectable extrahepatic disease and with the primary tumor in situ were accepted for inclusion. All patients underwent radiologic evaluation with at least a contrast computed tomography (CT) scan of the abdomen and chest for staging and for the exclusion of nonresectable extrahepatic disease. A CT-based volumetric analysis of the liver was performed in each patient before inclusion.

MEASUREMENTS AND ESTIMATES OF LIVER VOLUMES AND GROWTH RATES

The volume of the FLR was estimated as the volume of the part of the liver without tumors that would remain after the final surgery. If there were initially tumors in the FLR, the estimated volume lost from the resection or ablation of these was subtracted from the FLR to estimate the tumor-free FLR. The volumetric measurements were made according to the standards at each center. Volumes were measured manually at the University Hospital of Linköping, Sahlgrenska University in Gothenburg, Rikshospitalet in Oslo, and Skåne University Hospital in Lund.¹⁵ Volume Viewer (General Electrics, Fairfield, CT) was used at the Karolinska University Hospital in Stockholm. Philips Intellispace (Philips, Amsterdam, The Netherlands) was used at Rigshospitalet in Copenhagen.

The estimated total liver volume (eTLV) was calculated based on body surface area according to Mosteller.^{16,17} Standardized FLR (sFLR) volume was calculated as a percentage as follows: $[\text{FLR (mL)} / \text{eTLV (mL)}] \times 100 = \text{sFLR percentage}$.

To assess the rate of liver hypertrophy, the kinetic growth rate (KGR) was calculated as previously described.⁸

RANDOMIZATION

Patients were randomized 1:1 between the ALPPS and TSH treatment groups using computer-generated random numbers in blocks of 20 (10:10), each sealed opaque envelope contained the same number of papers. The randomization process was conducted by a certified research nurse at the headquarters in Linköping. No surgeons were involved in this process. The envelopes were distributed in numbering order to participating centers. Patients were screened for inclusion at the multidisciplinary tumor conference at each university hospital with all information regarding the inclusion factors available. Only patients with CRLM and a sFLR of less than 30% after neoadjuvant or conversion chemotherapy were considered for inclusion. There was no lower limit of sFLR for inclusion. Patients with progressive disease despite chemotherapy

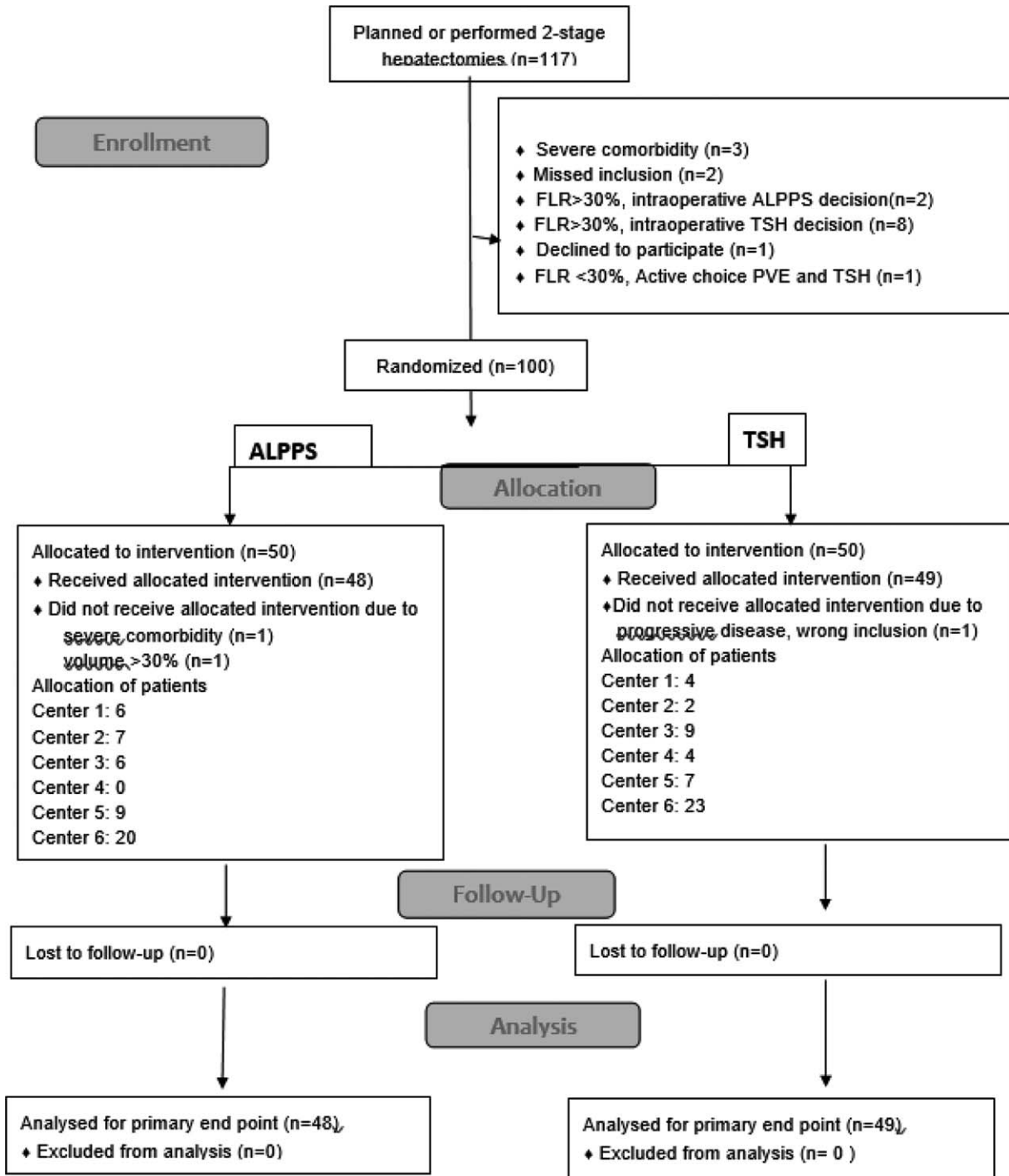


FIGURE 1. At the multidisciplinary tumor board meeting all the inclusion and exclusion criteria were available. Therefore, very few patients were excluded at the outpatients clinic at randomization. In the group not meeting inclusion criteria, 10 patients with FLR more than 30% were included. These were treated with ALPPS or TSH due to intraoperative findings of severe chemotherapy damage or additional metastasis not detected at the preoperative work up.

were excluded from the study. Patients could have extra hepatic disease and the primary tumor in situ provided that this was planned to be resected at a later stage. Patients with severe comorbidity were excluded from the study.

At an outpatient clinic, after the multidisciplinary tumor conference at each university hospital the patients were informed about the study, and after informed verbal and written consent, patients that fulfilled the inclusion criteria and accepted participation

were randomized. Envelopes were strictly drawn in numbered order at each center. The study was not blinded, and the patients were informed about the surgery they were randomized to.

SURGICAL PROCEDURES AND INTERVENTIONS

Each participating center had a long experience with liver vascular interventions and specifically portal embolization. The PVE techniques used in Linköping, Karolinska, and Oslo have previously been described.¹⁸ In Gothenburg and Lund, histoacryl/lipiodol (B Brown surgical SA, Rubi, Spain/Guerbet, Bloomington, IN) was used, with the addition of coils when needed. In Copenhagen, embospheres (Merit Medical Systems Inc., South Jordan, UT) were used. A right-sided PVE was used; segment 4 branches were embolized on demand. Of the 35 patients treated with portal embolization, 28 had histoacryl/lipiodol 1:4 and amplatz ± particles and 7 had embospheres.

Percutaneous portal embolization was used in all patients with no tumors in the FLR and, at the discretion of the center, in patients with metastasis in the FLR treated with local resections or ablation. Within each center the same methods were used for all patients, either PL at the time of local resections or PVE the day after.

Portal ligation was used in conjunction with local resections and/or ablations in the FLR. The second step in the TSH group was right or extended right hepatectomy.

The surgical approach used for ALPPS by 3 of the centers has been previously published, and a similar technique was used at the remaining centers.¹⁸ In all patients, a CT scan was performed on day 7 after primary intervention to calculate the sFLR. If the patients had not reached a FLR of 30%, new scans were performed on day 14 and day 28.

As soon as the liver reached a sFLR of at least 30% after PVE/PVL or stage 1 ALPPS, the patients were scheduled for the stage 2 operation.

DEFINITION OF TREATMENT FAILURE

For both groups, treatment failure occurred if the following conditions were observed:

1. Carcinomatosis or unexpected metastasis occurred, prohibiting radical resection.
2. Unexpected cirrhosis was found at operation.
3. Patients developed complications that prevented the second operation from being performed.

The condition of treatment failure specific to the TSH group was as follows:

1. If the KGR was below 2%/wk at any time and the liver had not reached a sFLR of $\geq 30\%$ after 8 weeks, then this was considered a failure of the treatment arm. Crossover to the ALPPS treatment was allowed.

The condition of treatment failure specific to the ALPPS group was as follows:

1. If the second operation could not be performed because the sFLR did not reach 30%, then this was considered a failure of the treatment arm. As long as the KGR was more than 2%/wk, the second operation could be postponed.

Blood Samples

Blood samples were collected before the first and second interventions for analysis of basic blood values.

STATISTICAL ANALYSIS

Sample size was calculated to detect a 25% increase in RRs, which was the primary endpoint.

The RR after PVE or portal ligation varied from 55% to 76%.¹⁹ The RR in the TSH arm was expected to be 65% due to the inclusion of patients with very small sFLRs.

Based on previously published ALPPS data, a RR of at least 90% was expected in this treatment arm.¹²

A Z test based on an alpha error of less than 0.05 and power of 80% revealed that a minimum of 43 patients were needed in each group. Therefore, 50 patients were included in each group.

Primary Outcome

With the primary endpoint being RR, a per protocol analysis was performed where the proportions of patients in each arm going through the whole treatment were compared using a chi-square test, with odds ratio and 95% confidence interval (CI). Patients crossing over from TSH to ALPPS were not counted as going through the treatment arm.

Secondary Outcomes

Complications

Complications during hospital stay and within 30 days after final intervention according to Clavien–Dindo classification¹³ were compared between the 2 treatment arms as a per protocol analysis. The proportion of patients with a score equal or above 3a were compared using Fischer exact test, with odds ratio and 95% CI.

Mortality

The proportion of 30 and 90 days mortality after final intervention in each treatment arm were analyzed both as intention to treat and per protocol using Fischer exact test with odds ratio and 95% CI.

Surgical Resection Margin in the Liver

Comparison of the proportion of microscopic negative surgical resection margin in the liver was performed as a per protocol analysis between the 2 groups using Fischer exact test with odds ratio and 95% CI.

For the comparison of continuous data, where normal distribution was assumed, a *t* test was used. For the comparison of continuous data, where normal distribution was not assumed, a Mann–Whitney test was used. The data are presented as the mean \pm SD. A *P* value of 0.05 or less was considered statistically significant. Statistical analyses were carried out using IBM SPSS Statistics 23 (IBM Corporation, Armonk, NY).

PATIENT DEMOGRAPHICS

Between June 2014 and August 2016, 117 patients were assessed for eligibility. Of those 117 patients, 100 were randomized (Fig. 1) to the ALPPS (50 patients) or TSH (50 patients) groups. Of these, 2 patients in the ALPPS group and 1 patient in the TSH group were excluded. The study population therefore included 97 patients, 48 in the ALPPS group, and 49 in the TSH group. The study population included 29 females and 68 males aged 65 ± 10 years. Baseline demographics are presented in Table 2.

ALPPS was not performed in any patient with CRLM with an initial FLR less than 30% outside the study during the study period at any of the including centers. One patient with an initial FLR less than 30% actively chose PVE and TSH. There were 10 patients with CRLM operated with ALPPS or TSH with an initial FLR more than 30% during the study period. Decision of treatment for all these patients were made intraoperatively due to chemotherapy induced

TABLE 2. Characteristics of Enrolled Patients

Characteristics	ALPPS (n = 48)	TSH (n = 49)	P
Age, yr	65.4 ± 8.9	64.9 ± 11.7	0.74
Male sex, no. (%)	32 (67%)	36 (73%)	0.46
BMI [†]	24.9 ± 3.3	26.4 ± 3.5	0.023
Primary tumor colon/rectum	28/20	29/20	0.93
Primary tumor resected (yes/no)	29/19	31/18	0.77
Number of metastasis 1–5/6–10/11– [‡]	16/21/11	15/15/19	0.21
Largest tumor at any time point (mm)	54 ± 41	49 ± 39	0.45
Suspected hilar lymph nodes (>10 mm)	4	2	0.40
Extrahepatic disease [§]	9	7	0.59
ASA 1/2/3	12/32/4	12/28/9	0.34
ECOG 0/1/2	28/17/3	30/19/0	0.20
Diabetes	6	6	0.97
Previous liver surgery	3	5	0.43
Method of staging radiology			
MRI	12	13	
CT	36	36	
Volume FLR (mL)	363 ± 85	365 ± 103	0.91
Volume FLR (%) of sTLV (sFLR)**	22.4 ± 4.3	21.2 ± 5.1	0.23
Blood values			
Hemoglobin (g/L)	132 ± 15	131 ± 16	0.62
White blood cells (10 ⁹ /L)	6.7 ± 2.0	6.2 ± 2.0	0.48
Platelets (10 ⁹ /L)	226 ± 65	231 ± 82	0.71
INR	1.0 ± 0.1	1.0 ± 0.1	0.59
Albumin (g/L)	37 ± 7	39 ± 5	0.48
Bilirubin (μmol/L)	10 ± 5	10 ± 7	0.99
Creatinine (μmol/L)	75 ± 15	76 ± 16	0.86
Sodium (μmol/L)	141 ± 3	141 ± 3	0.99
MELD score	7 ± 1	7 ± 1	0.25
Randomization to first intervention (d)	20 ± 13	18 ± 11	0.76
Preoperative chemotherapy ^{††}			
FOLFIRI	10	8	
5-FU	1	2	
FOLFOX	19	20	
XELOX	1	2	
FOLFOX+ab	3	4	
XELOX + ab	3	3	
FOLFIRI + ab	10	8	
Xeloda + ab	0	1	
Preop chemo cycles	6 ± 4	7 ± 4	0.20
Last dose to first intervention (d)	48 ± 28	49 ± 61	0.93
Response to chemotherapy [¶]			
Stable disease	9	10	0.80
Partial response	38	38	

*Plus-minus values are means ± SD.

†Body mass index is the weight in kilograms divided by the square of the height in meters.

‡Number of metastasis in each patient is counted as (1–5, 6–10, 11 or more).

§Metastasis in lungs or local recurrence of rectal cancer; MELD model of end-stage liver disease.

¶One patient in each group did not receive preoperative chemotherapy.

||Future liver remnant, the part of the liver that will remain after final resection.

**sFLR% relative volume in relation to the patients estimated total liver volume.

††One patient in each group did not receive preoperative chemotherapy.

FOLFOX indicates folinic acid, 5-FU, oxaliplatin; XELOX, capecitabine, oxaliplatin; FOLFIRI, folinic acid, 5-FU, Irinotecan; ab, bevacizumab or panitumumab or cetuximab.

severe liver damage (steatohepatitis/sinusoidal obstruction syndrome) or new metastasis not detected at the preoperative radiology.

PRIMARY OUTCOME

Of the 48 eligible patients in the ALPPS arm, 41 reached a sFLR more than 30% within 7 days, and another 3 reached a sFLR more than 30% within 14 days (92%) (Table 3).

In the TSH group, 28 (57%) of the patients reached 30% sFLR without tumor progression and therefore underwent the planned hepatectomy. Fourteen patients reached a FLR more than 30% after 7 days, and another 9 patients reached a FLR more than 30% after 4 weeks. The remaining 5 patients reached a FLR more than 30% within another 3 weeks. The RR was 92% in the ALPPS arm and 57% in the TSH arm ($P < 0.0001$).

SECONDARY OUTCOME

Complications and Radicality

When the protocols were compared, complications $\geq 3a$ based on the Clavien–Dindo classification were observed in 19 (43%) of the patients in the ALPPS group compared with 11 (43%) in the TSH group ($P = 1$) in the per-protocol analysis (Table 3).

Five patients in the ALPPS group were reoperated after the second operation due to intestinal obstruction ($n = 1$), wound rupture ($n = 2$), or bile leakage ($n = 2$). One patient in the TSH group was reoperated due to intestinal obstruction ($P = 0.25$). No differences in radicality were observed. Blood values measured before the first and second interventions are shown in Tables 2 and 3.

90-day Mortality After the Final Intervention

The 30-day mortality was one in each group. The 90-day mortality from the final intervention was 4 (9.1%) in the ALPPS group and 3 (10.7%) in the TSH group ($P = 0.64$) for the patients successfully treated (Table 2). The causes of mortality are listed in Table 4. None of the patients with fatal outcomes had a MELD score above 9 or an ALPPS risk score above 5 before the second intervention.²⁰

Four patients in the ALPPS and 2 in the TSH group had hilar lymph nodes resected during the first intervention. One patient in the ALPPS and 2 in the TSH group had their primary tumor resected during the first or the second intervention. None of these patients had any severe complications.

Treatment Length

The time from the first intervention to the last intervention was 11 ± 11 days in the ALPPS group compared with 43 ± 15 days in the TSH group ($P < 0.0001$) (Table 3). There was no difference between the 2 groups regarding the number of days in hospitals for the patients going through the full treatment.

CROSSOVER

Thirteen eligible patients (27%) in the TSH group were not successfully treated due to inadequate hypertrophy and did not reach a sFLR of 30% (Table 5). Of those patients, 12 (92%) could be treated via crossover to ALPPS. The remaining patient with insufficient liver growth also had tumor progression. The rescue ALPPS patients had their final resection 8 (8–16) days after the situ split. Adding the rescue ALPPS patients to the TSH arm increased the RR to 82%, which was still less than the RR of the ALPPS arm (92%), although the difference was not significant ($P < 0.1$).

Patients Failing to Reach sFLR 30% in the TSH Group

A subgroup analysis of the 14 patients with PVL versus the 35 patients with PVE showed that 43% versus 40%, respectively, failed to reach the second stage ($P = 0.42$). The corresponding numbers due to insufficient growth were 36% and 23% ($P = 0.36$). All but one of these patients failing to show sufficient liver growth had a final sFLR

TABLE 3. Interventions, Liver Growth, Complications, and Endpoints

Intervention 1	ALPPS (n = 48)	TSH (n = 49)	P
Number of metastasis at surgery	8 ± 4	8 ± 5	0.48
PVE		27	
PL + Local resection/ablation in FLR		14	
PVE + local resection/ablation in FLR		8	
ALPPS 1	18		
ALPPS 1 + local resection/ablation in FLR	30		
Bleeding during surgery	762 ± 660	141 ± 182	<0.0001
Liver growth after first intervention			
Volume 7 d FLR (mL)	605 ± 140	450 ± 140	<0.0001
Volume 7 d sFLR (%)	37.1 ± 7.5	26.1 ± 6.7	<0.0001
KGR days 0–7	14.1 ± 6.0	6.1 ± 5.4	<0.0001
Growth of FLR (mL/d)	35.4 ± 17.9	12.3 ± 8.6	<0.0001
Volume increase (mL)	237 ± 108	93 ± 67	<0.0001
Volume increase (%)	68 ± 38	36 ± 18	<0.0001
% Reached sFLR 30% after 7 d ^{**}	87	29	<0.0001
% reached sFLR 30% after 14 d	92	33	<0.0001
% Reached sFLR 30% after 28 d	92	47	<0.0001
Days from first to second intervention [†]	11 ± 11	43 ± 15	<0.0001
Blood values before second intervention			
Hemoglobin (g/L)	102 ± 13	124 ± 19	<0.0001
Platelets (10 ⁹ /L)*	302 ± 129	234 ± 89	=0.01
C-reactive protein (mg/L)	71 ± 50	23 ± 40	<0.0001
INR	1.2 ± 0.1	1.1 ± 0.1	=0.001
Albumin (g/L)	28 ± 5	37 ± 7	<0.0001
Bilirubin (μmol/L)	10 ± 7	9 ± 5	0.43
Creatinine (μmol/L)	64 ± 16	75 ± 15	=0.001
Sodium (μmol/L)	139 ± 3	140 ± 3	0.10
MELD	7 ± 1	7 ± 1	0.25
Intervention 2:	ALPPS (N=44)	TSH (N = 28)	
Right hepatectomy (RH)	23	12	
RH + local resection/ablation in FLR	2		
Extended right hepatectomy (ERH)	18	7	
ERH + local resection/ablation in FLR	1	8	
Bleeding during surgery (mL)	234 ± 454	1009 ± 658	<0.0001
Complications (Clavien–Dindo)			
Grade (% of the patients)			
Grade 2	(15/44)34	(10/28)36	0.89
Grade 3a	(10/44)23	(8/28)29	0.58
Grade 3b	(5/44)11	(1/28)4	0.24
Grade 4a	0	0	
Grade 4b	0	0	
Total length of stay ^{¶,§}	23 ± 17	18 ± 14	0.15
Readmitted after final surgery (%)	(12/44)27	(9/28)32	0.66
Primary end point:			Odds ratio, P
Resection rates [‡] (%)	(44/48)92	(28/49)57	8.25 (2.6–26.6) P<0.0001
Secondary end points:			
Complications grade ≥3a [§] (%)	(19/44)43	(12/28)43	1.01 (0.4–2.6) P = 0.99
90-d Mortality [§] (%)	(4/48)8.3	(3/49)6.1	1.39 (0.3–6.6) P = 0.68
90-d Mortality [§] (%)	(4/44)9.1	(3/28)10.7	0.83 (0.2–4.0) P = 0.82
Negative margin in the liver (%) ^{§,††}	(34/44)77	(16/28)57	2.55 (0.9–7.1) P = 0.11

*Plus–minus values are means ± SD.

†Surgically successfully treated patients.

‡Intention to treat.

§Per protocol.

¶Total length of stay, days in hospital during interventions after final intervention; R0 microscopically radical liver resection.

||Future liver remnant, the part of the liver that will remain after final resection.

**sFLR%, relative volume in relation to the patients estimated total liver volume, radiology was performed after 1, 2, and 4 weeks after primary intervention.

††Negative microscopic resection margin for all resected tumors in the liver.

KGR indicates kinetic growth rate, absolute increase in volume in % in one week; MELD, model for end-stage liver disease; ERH, formal right trisegmentectomies.

of less than 22% (Table 5). Five patients in the PVE group also had segment 4 embolized, only 2 of these were resected. Two had tumor progression and 1 had insufficient growth and crossed over to ALPPS.

DISCUSSION

This is the first randomized controlled trial (RCT) comparing traditional TSH with the ALPPS procedure for patients with an

TABLE 4. Ninety Days Mortality After Final Intervention

ALPPS Patients (n = 4)	MELD	Age	ASA	ECOG	Risk Points
(1) Day 9. Intestinal obstruction, liver failure, bleeding	6	72	2	0	4.9
(2) Day 33. Pulmonary embolism after first intervention, liver failure after final intervention, bile leak, MOF	6	68	2	1	4.1
(3) Day 53. Liver failure followed by bacterial infection	9	61	2	1	2.6
(4) Day 70. Technical failure causing bile duct stricture, bile leak, liver failure	7	66	1	0	2.3
TSH Patients (n = 3)					
(1) Day 9. Kidney failure, liver failure	8	70	3	1	4.7
(2) Day 38. Bile leak, liver failure, MOF	6	63	1	0	2.9
(3) Day 59. Tumor progression, liver failure, MOF	6	75	3	1	4.8

The model predicts mortality risk including tumor type, age, interstage complication, creatinine, and bilirubin; 5%, 10%, and 20% mortality risk for scores 3.9, 4.7, and 5.5 respectively.²⁰

MOF indicate multiple organ failure; MELD, model of end-stage liver disease, estimated the day before the final intervention; ECOG, Eastern Cooperative Oncology Group; Risk Points, ALPPS risk points before final intervention.

advanced tumor burden due to CRLM and an insufficient FLR, where no other curative alternatives are available.²¹ The present study shows that RRs are significantly higher with ALPPS than with TSH, with similar rates of severe complications, mortality, and negative surgical margins in the liver.

The RR was close to the expected value in the ALPPS group, whereas it was lower than expected in the TSH group, with an RR of 57% compared with 60% to 75% as reported in previous studies.^{5–8,22} This may be due to the inclusion of patients with very small FLRs and the KGR requirement of more than 2%/week. Another explanation is the requirement to reach a sFLR of 30%, which is higher than what has been required in some other studies.⁸ The reason for our volume requirement was the fact that patients received preoperative chemotherapy, which may impair liver function.²³ A lower cutoff of 25% sFLR would have increased the success rate of the TSH group (by 1 patient) to 60%. We found no difference in liver growth or RRs between PL or PVE patients, indicating that either method was not the reason for the RRs.

TABLE 5. Failures of TSH

Patients Failing TSH (n = 21) and Crossover to ALPPS (n = 13)	P
Failing due to tumor progression (n = 8)	
PVL patients (2/14)14%	0.81
PVE patients (6/35)17%	
Failing due to insufficient growth (n = 13)	
PVL patients (5/14)36%	0.36
PVE patients (8/35)23%	
Baseline volume FLR* [‡] (mL)	276 ± 77
Baseline volume sFLR [†] (%)	16.3 ± 4.5
Volume 7 d FLR (mL)	342 ± 89
Volume 7 d sFLR (%)	20.4 ± 5.2
KGR days 0–28	1.1 ± 0.6
Volume increase (%) days 0–7	28.6 ± 10.3
Crossover from TSH to ALPPS (n = 13)	
Successful ALPPS	12
Days from First intervention to ALPPS 1	85 ± 82
Complication ≥3a (%)	27
Negative surgical margin in the liver (%)	67
90-d mortality after final intervention	0

*Future liver remnant, the part of the liver that will remain after final resection.

[‡]sFLR% relative volume in relation to the patients estimated total liver volume.

[†]Plus-minus values are means ± SD.

PVE indicates portal venous embolization; PL, portal ligation; FLR, future liver remnant; KGR, kinetic growth rate, absolute increase in volume in % in 1 week.

Previous studies have reported a RR of 98% in the ALPPS group.¹² Four patients experienced treatment failure in our study due to insufficient liver hypertrophy, vascular injury during surgery, advanced tumor burden, and cirrhosis. This indicates a level of RR similar to what was expected.

As expected and in agreement with previous findings,⁴ liver hypertrophy was faster and more pronounced in the ALPPS group than in the TSH group. Therefore, the timeframe for completing ALPPS was shorter.

Perioperative mortality remained high in both groups, indicating that less invasive alternatives may be considered. When properly investigated, the laparoscopic approach,²⁴ microwave ablation along the division line,²⁵ or partial ALPPS may prove to be advantageous.²⁶

The 90-day mortality rates did not differ between the groups and were comparable to previously reported 90-day mortality rates.¹² The patients with fatal outcomes in the ALPPS group did not have impaired MELD scores but were all older than 60 years of age, which is a previously proposed risk factor.¹² The majority of the patients in this study were older than 60 years of age.

The patients in the TSH group that did not reach a sFLR of 30% were offered ALPPS, making this an important rescue alternative, as previously proposed.²⁷

Although this trial has the benefit of general applicability, which is the main inherent strength of multicenter RCTs, some limitations must be acknowledged. Resectability was evaluated at each center, and the results may differ. Similarly, the volumetric methods used were those routinely used at each center and were, therefore, not standardized. However, each patient was compared with him/herself in serial measurements; thus, the results may be considered reliable. Also, the method of portal embolization differed between the centers, but the success or growth rate did not.

CONCLUSIONS

Compared with the use of TSH, the use of ALPPS for patients with CRLM resulted in a higher RR without a higher 90-day mortality rate, a higher rate of severe complications or a lower rate of negative surgical margins in the liver. ALPPS is therefore applicable when no other treatment option is available. Still, long-term outcomes remain to be elucidated and therefore the role of ALPPS regarding oncological outcome remains uncertain.

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