Randomized Controlled Trial

ANNALS OF SURGERY OPEN

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Long-Term Follow-Up of Patients with Advanced Colorectal Liver Metastasis

A Survival Analysis from the Randomized Controlled Multicenter Trial LIGRO

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Objective: The objective of this study was to evaluate the long-term oncological outcomes of patients with colorectal liver metastasis (CRLM) randomized for associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) or 2-stage hepatectomy (TSH).

Introduction: For advanced CRLM, TSH or ALPPS may be needed for tumor freedom. The randomized, controlled, multicenter trial LIGRO showed an increased resection rate in patients who underwent ALPPS but no difference in morbidity or mortality. The 2-year survival analysis revealed better overall survival in the ALPPS group. Here, the long-term survival analysis from the LIGRO trial is reported.

Methods: In the LIGRO trial, 100 patients were randomized to TSH or ALPPS, with the option of rescue ALPPS if insufficient growth was found after the initial step of TSH. Patients were enrolled between June 2014 and August 2016. Follow-up data for this study were collected between November 2022 and February 2023.

Results: In total, 16 patients were alive at the end of the follow-up period. The estimated median follow-up time was 93 months. Estimated median overall survival times were 45 months in the ALPPS group and 27 months in the TSH group (P = 0.057), with 5-year survival rates of 31% and 20%, respectively. Positive prognostic factors were liver tumor-free status at the first follow-up and rectal primary tumor. Negative prognostic factors were extrahepatic disease and increasing CLRM size.

Conclusion: Liver tumor-free status is a predictor of long-term survival, along with extrahepatic disease, large CRLM size, and rectal primary tumor. Survival did not significantly differ between patients treated with ALPPS or TSH.

INTRODUCTION

Colorectal cancer is the third most common and the second most deadly cancer worldwide.[1] The liver is the dominant metastatic site for colorectal cancer metastasis.[2] The remarkable hypertrophic abilities of the liver have been known since the 1920s when this was first studied in animal models.[3] As a method for expanding surgical treatment of liver malignancies, its routine implementation was proposed in the 1980s and 1990s.[4,5] Augmentation of liver volume has since become the clinical standard in patients undergoing major hepatectomies in which the future liver remnant (FLR) is too small and postoperative liver failure is anticipated. For a normal healthy liver, a standardized FLR (sFLR) of a minimum of 20% is recommended. After preoperative chemotherapy, a sFLR of 30% is recommended; in the setting of preexisting liver disease, such as cirrhosis, 40% sFLR is recommended.[6,7] Two-stage hepatectomy (TSH) with portal vein embolization (PVE) or portal vein ligation (PVL) are well-established methods for inducing hypertrophy in the FLR, and the associated 3-year survival rate is greater than 50%.[8] A newer technique is "Associating Liver Partition and Portal vein ligation for Staged hepatectomy" (ALPPS), a 2-stage surgical intervention discovered by chance in 2007.[9,10] In ALPPS, PVL is combined with an in situ split of the liver parenchyma in the first stage, with liver resection being performed in the second stage. ALPPS induces rapid hypertrophy of the FLR, thus potentially shortening the time to radical hepatectomy compared with TSH.[11,12] Earlier concerns about ALPPS included the high morbidity and mortality associated with the procedure, with complication rates up to 70%.[12–14] However, careful patient selection and risk adjustment can reduce postoperative complications and mortality.[15] The prospective randomized multicenter LIGRO trial of patients with advanced colorectal liver metastases (CRLM) showed no difference in morbidity or mortality between patients treated with ALPPS and those treated with TSH but did demonstrate increased resection rates in the former group.[16] With the shift toward better patient selection and declining complications, more focus has been placed on

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Disclosure: The authors declare that they have nothing to disclose.

All authors participated in the research design, performance of the research, data analysis, and writing of the paper.

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Annals of Surgery Open (2024) 3:e455

Received: 23 April 2024; Accepted 27 May 2024

Published online 26 June 2024

DOI: 10.1097/AS9.0000000000000455

oncological results. Nonetheless, available survival data are conflicting, as some studies have shown shorter survival after ALPPS than after TSH,[17] whereas the first survival analysis of the LIGRO trial indicated better overall survival (OS) for patients treated with ALPPS.[18]

This is the second analysis of oncological outcomes of the prospective, randomized controlled LIGRO trial involving patients treated with ALPPS or TSH and followed for at least 6 years.[16]

METHODS

This study is the second planned analysis of survival data from the LIGRO trial, a Scandinavian multicenter randomized controlled trial (ClinicalTrials.gov, NCT02215577). An extensive description of the LIGRO study has been previously published.[16] The inclusion criterias were patients with surgically unresectable CRLM due to sFLR <30% and stable disease or response to neoadjuvant chemotherapy. The exclusion criterias were progressive disease on neoadjuvant chemotherapy, cirrhosis, unresectable extrahepatic disease, substantial comorbidity rendering patients unsuitable for major hepatic surgery, and age <18 years. In total, 100 patients were included, with the first patient being included in June 2014 and the last in August 2016. Patients were randomized to ALPPS or TSH, with 50 patients in each group. The preoperative liver volume was estimated using computed tomography (CT) or magnetic resonance imaging (MRI). The FLR was defined as the tumor-free liver volume that remained after the completion of radical hepatectomy. Patients randomized to the ALPPS group were treated with classical ALPPS, and the parenchyma was completely transected at the first intervention. Patients randomized to the TSH group were treated with PVE or PVL. Rescue ALPPS was allowed for patients in the TSH group with insufficient FLR growth (sFLR <30%). Metastases in the FLR were treated with local resection or ablation, depending on the size of the lesion and its location in the liver, and at the discretion of the treating center professionals.

The first planned analysis of 2-year survival data has previously been published[18] and contains an in-depth description of the methodology used for the follow-up procedures. Follow-up data for this study were collected from November 2022 to February 2023. For a flow chart of the LIGRO trial, see Figure 1.

Follow-Up

The first follow-up was at 4 weeks after surgery and approximately 4, 8, 12, 18, and 24 months after surgery. Follow-up was individualized after 2 years. Only 1 patient was lost to follow-up due to emigration.

Most patients were discussed by a postoperative multidisciplinary tumor board, and patients were referred to medical oncology for adjuvant chemotherapy at the first follow-up. The final decision to proceed with chemotherapy was made in the meeting between the patient and oncologist. If a primary tumor or other metastases were present after liver surgery, resection or other appropriate treatments were considered. Liver tumor-free status and overall tumor-free status were considered if no tumor was evident on follow-up CT or MRI. Patients with recurrent disease were discussed by a multidisciplinary tumor board, and patients were considered for surgery, other interventions, chemotherapy, or best supportive care.

Scoring Systems

To calculate the total burden of tumors in the liver, the tumor burden score (TBS) for colorectal liver metastasis was calculated according to Sasaki et al.[19]

For the correlation of comorbidity and survival, the comprehensive ALPPS preoperative risk assessment (CAPRA) score was calculated according to Capobianco et al.[20] This score was also calculated for patients who underwent TSH because rescue ALPPS was an alternative in the study design.

Statistical Analysis

Continuous data were compared by the *t* test or analysis of variance. The results are expressed as medians [95% confidence interval (CI)], medians (min–max), or means (±SD). Categorical data were analyzed using the χ^2 test. The length of follow-up was analyzed using the reversed Kaplan–Meier method.[21] Unless stated otherwise, the starting point for follow-up was set at the first intervention (PVE/PVL or ALPPS stage 1). Survival was analyzed using the Kaplan–Meier method and log-rank test. OS was analyzed using the intention-to-treat principle (randomized to ALPPS or TSH) and per protocol (patients undergoing resection). Cox regression was used for univariable and multivariable analyses. Variables with $P < 0.10$ in univariable analysis were included in the multivariable analysis.

$P < 0.05$ was considered to indicate statistical significance.

All statistical analyses were performed using IBM SPSS Statistics, version 29.0.0.0 (IBM Corp, Armonk, NY).

Ethical Approval

Ethical approval was obtained from all participating countries.

RESULTS

Of the 50 patients in each group, 97 underwent intervention: 48 in the ALPPS group and 49 in the TSH group. Three patients were excluded because of severe comorbidities, initial sFLR >30%, or progressive disease. The baseline characteristics were previously published, and no differences were noted between the groups.[18]

At the end of the previous follow-up, 43 patients were alive. Between this and the previous study period, 1 patient was lost to follow-up due to emigration. At the end of the study period for the current analysis, 16 patients were still alive—11 in the ALPPS group and 5 in the TSH group—1 of whom was treated with rescue ALPPS. Of the surviving patients, 11 were considered tumor-free at the end of the previous analysis, 2 had recurrent disease, 1 was treated with palliative chemotherapy, and 2 had evidence of recurrence without treatment. At the end of the current follow-up, 4 patients had new recurrent disease. One patient underwent new liver resection, liver ablation, and stereotactic body radiation therapy involving the brain and lung. One patient underwent resection of metastasis in the abdominal wall, and another 2 patients underwent liver ablation. Two patients received chemotherapy; 1 patient underwent surgery for sarcoma and sarcoma lung metastases. The data for all surviving patients are summarized in Table 1.

Of the 27 patients who died since the previous follow-up, all but 2 had evidence of recurrent disease. One patient underwent local ablative treatment for new liver metastasis, 7 patients received stereotactic body radiation therapy for bone or brain metastases, 2 patients underwent lung surgery, and 1 patient underwent surgery due to local rectal recurrence. In total, 19 patients received palliative chemotherapy. In 2 patients, noncancer-related death occurred, and these patients were considered tumor-free at the time of their death.

The estimated median follow-up was 93 months (95% CI = 88–98). The estimated median survival time was 45 months (95% CI = 38–52) for patients randomized to the ALPPS group and 27 months (95% CI = 16–38) ($P = 0.057$) for patients randomized to the TSH group, Figure 2.

The estimated median OS after the diagnosis of CRLM was 52 months (95% CI = 47–57) in the ALPPS group and 38 months (95% CI = 30–46) in the TSH group ($P = 0.033$).

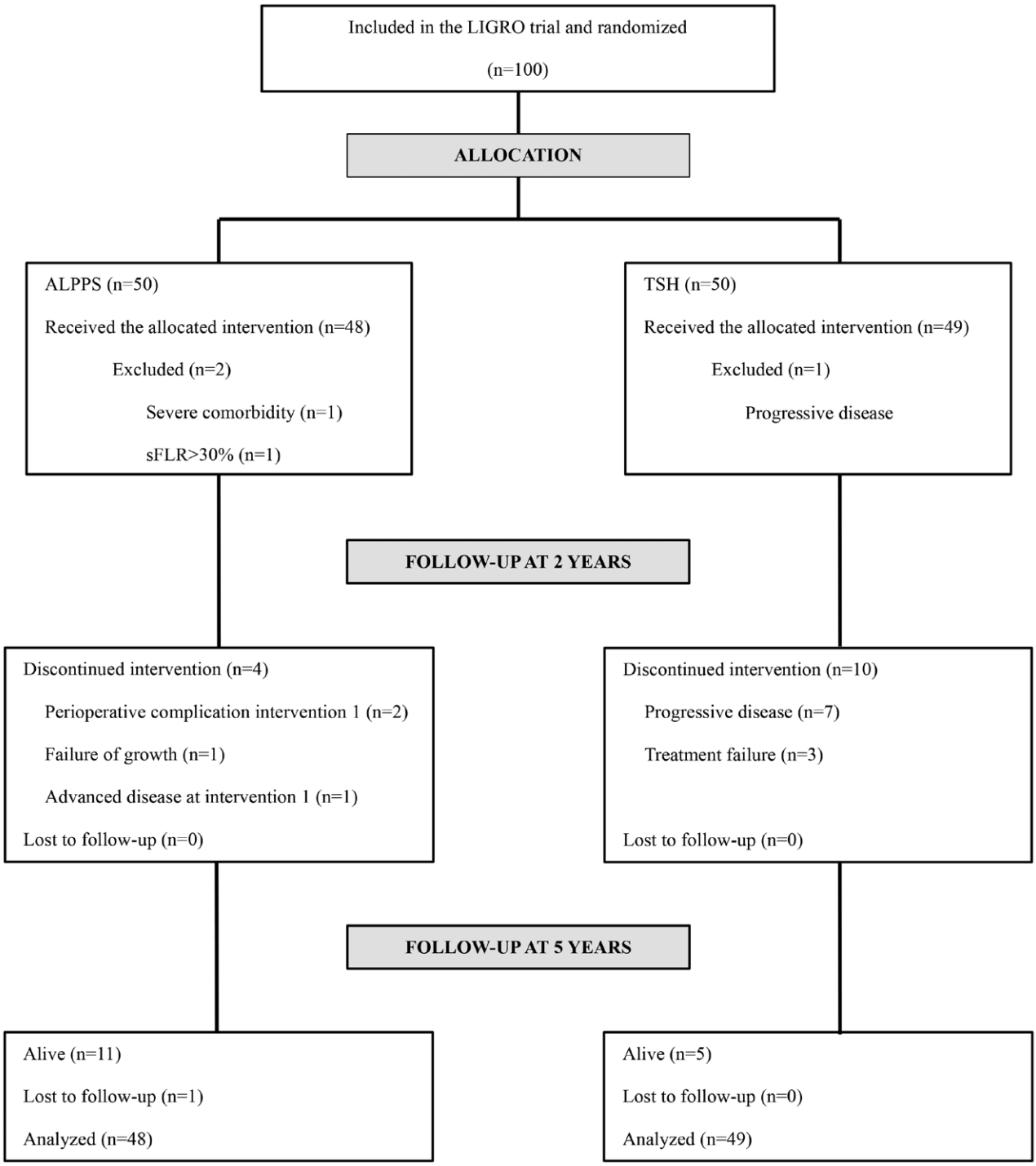


FIGURE 1. Flowchart of the LIGRO trial. Discontinued intervention describes patients completing step 1 of the allocated treatment, but not step 2.

Five year survival rate was 31% in the ALPPS group and 21% in the TSH group.

Outcome After Liver Resection

The estimated median survival after resection in the ALPPS group was 45 months (95% CI = 37–53). In the TSH group, 27 patients underwent resection with TSH, and 12 patients underwent resection after conversion to rescue ALPPS. The estimated median survival times were 38 months (95% CI = 30–46) and 27 months, respectively (95% CI = 25–29) (P = 0.130), Figure 3.

For patients who underwent resection, the estimated median survival after diagnosis of CRLM was 52 months (95% CI = 47–57) in the ALPPS group and 40 months (95% CI = 33–47) in the TSH group (P = 0.201).

Non-Resected Patients

For patients who did not undergo resection, the estimated median survival was 13 months (95% CI = 1–25), with no difference between the ALPPS and TSH groups, Figure 3. The reasons for not proceeding to resection were insufficient liver hypertrophy, progression of metastasis or complications related to the intervention.

TABLE 1.

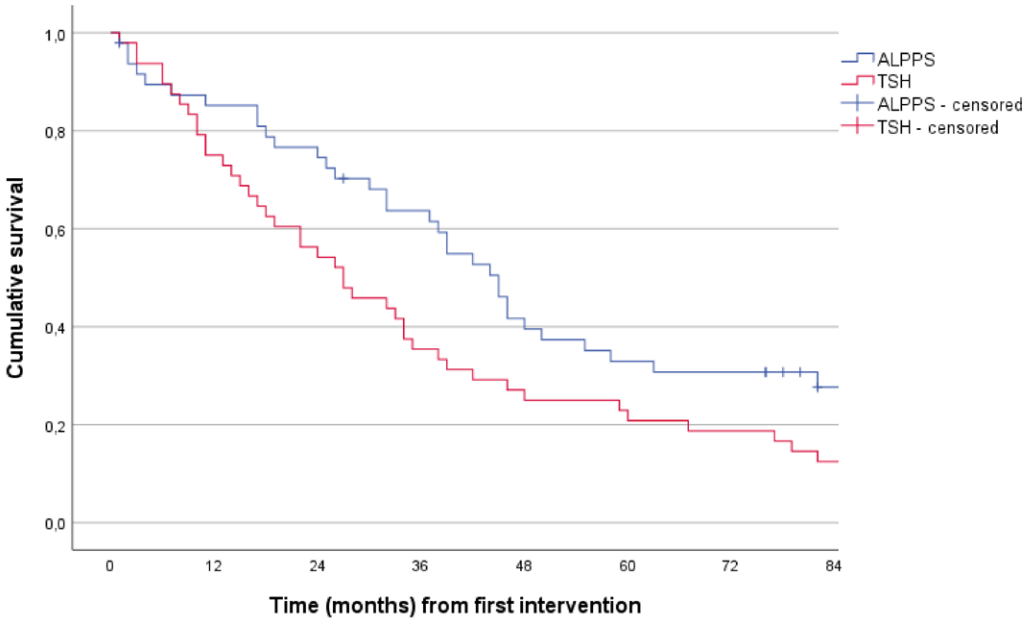
Summary of All Surviving Patients at the End of the Follow-Up Period

	Age	Sex	ASA Score	CAPRA	Primary Tumor, Stage	Number of CRLM	Largest CRLM (cm)	TBS	Tumor in FLR (n)	Extrahepatic Disease	Preoperative Chemotherapy*	Response to Chemotherapy	Surgery	Radical Resection Performed	R0/R1 in the Liver	Tumor Free at First Follow-Up	Tumor free at any time	Recurrence
1	55	Female	1	3.83	Left colon, T3N0	5	5.5	7.43	0	Yes	FOLFOX	Regression	ALPPS	Yes	R0	Yes	Yes	Liver, lung, brain
2	80	Male	2	6.04	Rectal, no staging	5	2.8	5.73	1	No	FLOX	Regression	ALPPS	Yes	R0	Yes	Yes	Liver
3	59	Male	2	6.17	Rectal T3N1	8	5.5	9.71	2	No	FLOX/FLIRI + panitumumab	Regression	ALPPS	Yes	R0	Yes	Yes	No
4	68	Male	1	5.00	Right colon, T3N1	10	2.5	10.31	1	No	FLOX	Regression	ALPPS	Yes	R1	Yes	Yes	No
5	68	Male	2	4.83	Sigmoid, T3N0	8	5.1	9.49	3	No	FLOX/FLIRI + panitumumab	Regression	ALPPS	Yes	R0	Yes	Yes	No
6	77	Female	2	6.32	Sigmoid, T3N0	7	3.8	7.96	0	No	FOLFIRI	Regression	ALPPS	Yes	R1	Yes	Yes	Liver
7	59	Male	2	1.36	Right colon, T3N0	1	2.0	2.24	0	No	FLOX	Stable disease	TSH	Yes	R0	Yes	Yes	No
8	54	Male	1	1.22	Rectal, T3N2	2	3.0	3.61	0	No	FLOX	Regression	TSH	Yes	R0	Yes	Yes	No
9	75	Male	2	3.59	Rectal, no staging	3	4.1	5.08	0	No	Xeloda/FOLFIRI + panitumumab	Regression	TSH	Yes	R1	Yes	Yes	No
10	53	Male	2	3.29	Rectal, T3N0	8	10.8	13.44	0	No	FOLFOX	Regression	ALPPS	Yes	R0	Yes	Yes	Multiple sites
11	73	Male	2	5.42	Right colon, T4N1	7	2.5	7.43	1	No	FLOX	Regression	Rescue ALPPS	Yes	R0	Yes	Yes	No
12	67	Male	2	4.59	Rectal, T3N0	12	5.0	13.00	4	No	FOLFOXIRI + panitumumab	Regression	ALPPS	Yes	R0	No	Yes	Liver
13	44	Female	2	2.93	Rectal, T3N2	4	4.5	6.02	1	No	CAPOX/FOLFOX + bevacizumab	Stable disease	ALPPS	Yes	R1	Yes	Yes	No
14	67	Male	2	6.80	Right colon, T3N1	13	3.8	13.54	0	No	FOLFOX + bevacizumab	Regression	ALPPS	Yes	R0	Yes	Yes	Abdominal wall
15	68	Female	1	2.95	Rectal, T3N1	2	5.0	5.39	0	No	No chemotherapy		TSH	Yes	R0	Yes	Yes	No
16	63	Male	2	4.35	Rectal, T3N1	2	10.0	10.20	0	No	FLIRI + panitumumab	Regression	ALPPS	Yes	R0	Yes	Yes	No
	Mean (SD)	Male/ Female (%)	ASA 1/2/3 (%)	Mean (SD)	Rectal Tumor (%)	Median (min–max)	Mean (SD)	Mean (SD)	No tumor in FLR (%)	Yes (%)				Yes (%)	R0 (%)	Yes (%)	Yes (%)	
Survivors	64.5 (9.8)	75/25	25/75/0	4.29 (1.68)	56	5 (1–13)	4.7 (2.5)	8.16 (3.44)	56	6				100	75	94	94	
Deceased	63.4 (10.4)	70/30	24/62/14	3.78 (2.10)	29	7 (1–23)	5.3 (4.3)	10.85 (5.19)	35	19				81	71	69	55	
P value	0.694	0.772	0.275	0.360	0.046	0.586	0.453	0.051	0.157	0.291				0.067	1.000	0.059	0.004	

A statistically significant difference was detected between survivors and deceased patients regarding the primary tumor site and tumor freedom at any time; a majority of the survivors experienced regression after preoperative chemotherapy.

*FOLFOX, fluorouracil + calcium folinate + oxaliplatin; FLOX, fluorouracil + calcium folinate + oxaliplatin; FLIRI, fluorouracil + calcium folinate + irinotecan; FOLFIRI, fluorouracil + calcium folinate + irinotecan; CAPOX, capecitabin + oxaliplatin; FOLFOXIRI, fluorouracil + calcium folinate + oxaliplatin + irinotecan.

ASA indicates American Society of Anesthesioloists.



Number at risk								
ALPPS	48	40	35	29	18	15	14	8
TSH	49	36	26	17	12	10	9	6

FIGURE 2. The estimated median survival time was 45 months for patients randomized to the ALPPS group (95% CI = 38–52) and 27 months (95% CI = 16–38) for patients randomized to the TSH group (P = 0.057).

Patients With Extrahepatic Disease

Upon inclusion in the LIGRO trial, 9 patients in the ALPPS group had extrahepatic disease, and an additional 2 patients had lung metastases resected before inclusion. In the TSH group, seven patients had extrahepatic disease at the time of inclusion. The most common site was the lungs. For patients with extrahepatic disease, the estimated median survival was 37 months (95% CI = 0–75) in the ALPPS group and 26 months (95% CI = 0–59) in the TSH group (P = 0.613). At the end of the current study period, only 1 patient with extrahepatic disease, who was randomized to the ALPPS group, was still alive.

For patients without extrahepatic disease, the estimated median survival was 48 months (95% CI = 39–57) in the ALPPS group and 27 months (95% CI = 18–36) in the TSH group (P = 0.059).

Disease-Free Survival

Among the patients who were considered disease-free at any time, after liver surgery, after primary tumor surgery, or after treatment for the extrahepatic disease, the estimated median disease-free survival was 10 months (95% CI = 8–12) in the ALPPS group and 7 months (95% CI = 5–9) in the TSH group, Figure 4. No statistical significance was detected (P = 0.461).

Survivors at the End of the Study Period

At the end of the study period, 16 patients were still alive. A summary of the characteristics of the patients can be found in Table 1. Basic patient characteristics, such as sex, age, and American Society of Anesthesioloists physical status classification system (American Society of Anesthesioloists score), did not differ between long-term survivors and deceased patients. Twelve of the 16 long-term survivors were treated with ALPPS. A significantly greater percentage of patients with rectal tumors, and greater tumor freedom at any time, were found among long-term survivors. A majority of the survivors experienced regression after preoperative chemotherapy.

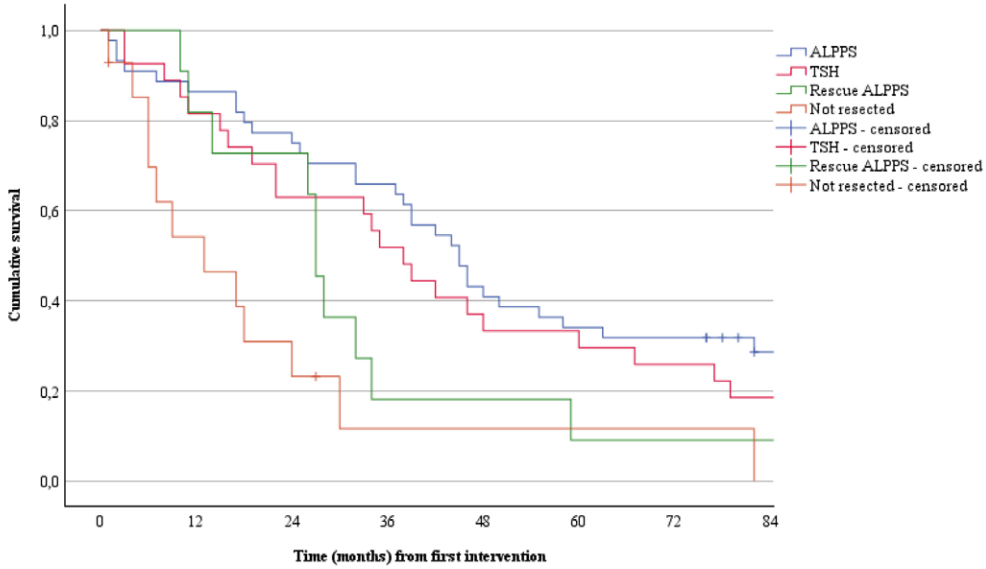
No significant difference in the CAPRA score was found between long-term survivors and deceased patients. However, notably, the mean CAPRA score was greater for survivors, and 4 of the 16 patients had a CAPRA score above 5.5, which indicates a 90-day mortality probability of 20%.

When comparing long-term survivors to all deceased patients and examining the following factors: extrahepatic disease, FLR tumor status, lack of radical resection, lack of tumor-free status at the first follow-up, no tumor freedom at any time, R1 resection, and no regression after neoadjuvant chemotherapy, the results showed that no long-term survivors had a combination of more than 3 of these 7 negative prognostic factors.

Univariable and Multivariable Survival Analyses

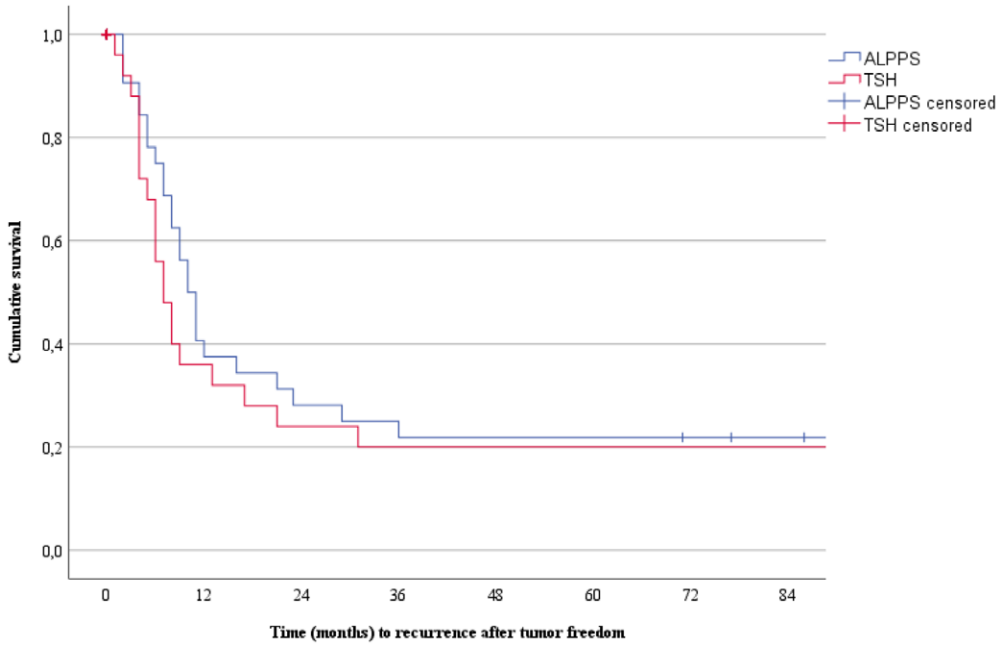
Univariable survival analysis via Cox regression revealed that 7 different parameters had a statistically significant impact on survival: unresected liver metastasis (HR = 2.441; 95% CI = 1.353–4.403; P = 0.003), size of the largest liver metastasis (HR = 1.092; 95% CI = 1.030–1.159; P = 0.003), severe postoperative complications (HR = 2.176; 95% CI = 1.278–3.706; P = 0.004), tumor-free status in the liver at first follow-up (HR = 0.429; 95% CI = 0.257–0.717; P = 0.001), tumor freedom at any time (HR = 0.314; 95% CI = 0.193–0.511; P < 0.001), primary rectal tumor (HR = 0.520; 95% CI = 0.305–0.885; P = 0.016) and TBS (HR = 1.066; 95% CI = 1.022–1.111; P = 0.003) (Table 2).

In multivariable analysis, 4 factors were shown to have a statistically significant impact on survival. Extrahepatic disease (HR = 3.447; 95% CI = 1.399–8.496; P = 0.007) and increasing size of the largest liver metastasis (HR = 1.254; 95% CI = 1.134–1.387; P < 0.001) had negative impacts on survival, whereas liver tumor-free status at the first follow-up (HR = 0.351; 95% CI = 0.168–0.732; P = 0.005) and a



Number at risk								
ALPPS	44	38	33	29	18	15	14	8
TSH	27	22	17	14	9	8	7	5
Rescue ALPPS	12	9	8	2	2	1	1	1
Not resected	14	7	3	1	1	1	1	0

FIGURE 3. OS of all randomized patients. The estimated median survival time after resection in the ALPPS group was 45 months (95% CI = 37–53). In the TSH group, 27 patients underwent resection with TSH, and 12 patients underwent resection after conversion to rescue ALPPS; the estimated median survival times were 38 months (95% CI = 30–46) and 27 months (95% CI = 25–29), respectively. For patients who did not undergo resection, the estimated median survival was 13 months (95% CI = 1–25) (*P* = 0.001).



Number at risk								
ALPPS	48	12	9	7	7	7	6	5
TSH	49	9	6	5	5	5	5	5

FIGURE 4. Disease-free survival after tumor resection. The estimated median disease-free survival was 10 months in the ALPPS group (95% CI = 8–12) and 7 months (95% CI = 5–9) in the TSH group (*P* = 0.461).

primary rectal tumor (HR = 0.352; 95% CI = 0.167–0.741; *P* = 0.006) were both associated with improved survival. Factors not significantly impacting survival included allocated treatment (ALPPS/TSH), response to preoperative chemotherapy, nonradical liver resection, right-sided colon tumor, and T4 primary tumor stage.

TABLE 2.

Cox Regression Analysis of Factors Associated With Survival According to Intention-to Treat

	Univariable Analysis				Multivariable Analysis*			
Covariable	**Coefficient**	**HR**	**95% CI**	***P* value**	**Coefficient**	**HR**	**95% CI**	***P* value**
Allocated treatment (ALPPS/TSH)	–0.430	0.651	0.415–1.021	0.062				
Response to chemotherapy (regression/stable)	–0.336	0.715	0.414–1.233	0.228				
Number of cycles of preoperative chemotherapy	0.007	1.007	0.951–1.066	0.819				
Extrahepatic disease	0.517	1.677	0.944–2.979	0.078	1.238	3.447	1.399–8.496	0.007
Liver metastasis not resected	0.892	2.441	1.353–4.403	0.003				
Age (decades) at diagnosis of liver metastasis	0.046	1.047	0.854–1.283	0.661				
ASA score	0.245	1.277	0.877–1.860	0.202				
Size (cm) of the largest liver metastasis	0.088	1.092	1.030–1.159	0.003	0.226	1.254	1.134–1.387	<0.001
Number of liver metastases	0.037	1.038	0.996–1.082	0.078				
Metastasis in the FLR	0.340	1.406	0.868–2.276	0.166				
Time (weeks) between intervention 1 and 2	0.027	1.027	0.992–1.064	0.128				
Postoperative complication CD ≥3a†	0.777	2.176	1.278–3.706	0.004				
Tumor-free in liver at first follow-up	–0.846	0.429	0.257–0.717	0.001	–1.047	0.351	0.168–0.732	0.005
Tumor-free at any time	–1.159	0.314	0.193–0.511	<0.001				
Nonradical (R1) liver resection	0.136	1.146	0.640–2.051	0.648				
Primary tumor right colon	0.215	1.240	0.721–2.132	0.436				
Primary tumor left colon	0.458	1.581	0.977–2.556	0.062				
Primary tumor rectal	–0.654	0.520	0.305–0.885	0.016	–1.045	0.352	0.167–0.741	0.006
Primary tumor T4	0.275	1.316	0.751–2.307	0.337				
N-status primary tumor	0.050	1.051	0.587–1.885	0.866				
Tumor burden score	0.064	1.066	1.022–1.111	0.003				

*Only variables with $P \leq 0.05$ are reported.

†Highest grade of complication after intervention 1 or intervention 2.

ASA indicates American Society of Anesthesioloists.

DISCUSSION

The LIGRO trial is the first and, to our knowledge, the only randomized controlled trial comparing ALPPS with TSH for patients with an advanced tumor burden of colorectal liver metastasis. The initial analysis of the LIGRO trial by Sandström et al.[16] revealed a significantly greater resection rate for ALPPS than for TSH, with similar rates of severe complications and mortality. In the first survival analysis of the LIGRO trial by Hasselgren et al.,[18] the patients in the ALPPS group exhibited a significantly longer median survival time than did those in the TSH group, with no difference in severe morbidity or 90-day mortality.

In this analysis, we found that tumor-free status in the liver at the first follow-up and the presence of a rectal primary tumor were positive prognostic factors for long-term survival. Extrahepatic disease and larger size of liver metastasis were both negative prognostic factors. With an estimated median follow-up time of 93 months, the numerical data suggest a survival benefit for the ALPPS group, though this difference was not statistically significant.

According to the Kaplan–Meier plots and numbers for OS, the results suggest an advantage for long-term survival in patients treated with ALPSS, albeit not significantly. The results might have reached statistical significance if more patients were included in the study and/or the follow-up was longer.

No difference was observed regarding disease-free survival, considering all recurrences, regardless of organ site, for patients considered to be tumor-free after treatment for the primary tumor, CRLM, and/or EHD. The disease-free survival data reported herein are in line with those of the registry study by Petrowsky et al.[22]

Patients treated with rescue ALPPS had worse prognosis than those treated with upfront ALPPS. This may be due to the prolonged waiting time between the first intervention and final resection to achieve a tumor-free liver, severe complications associated with stage 1 of the ALPPS procedure and/or failure to reach sFLR >30%. Patients who did not undergo resection had the least favorable outcome in terms of long-term survival, highlighting the importance of performing radical liver resection.[23,24]

Univariable analysis revealed 7 parameters that had a statistically significant impact on survival: unresected liver metastasis, increasing size of largest liver metastasis, severe postoperative complications, and increasing TBS were associated with poorer prognosis, whereas tumor-free status in the liver at the first follow-up, tumor freedom at any time and rectal primary tumor were associated with better prognosis.

Nonresection of CRLM and an increase in the size of CRLM were associated with poorer long-term survival in our study, consistent with the findings of previous studies.[23,25] The poorer prognosis may be due to a greater tumor burden in the liver, as indicated by a greater TBS, greater tumor burden in general, and/or more aggressive tumor biology with a greater risk of disseminated disease. This may also be reflected by the fact that our study revealed a poorer prognosis for patients with extrahepatic disease, in line with the findings of other publications.[23,24] R1 resection, however, was not a significant prognostic factor.

In a previous registry study by Petrowsky et al.,[22] T4 stage of the primary tumor and right-sided colon primary tumor were found to be independent risk factors for reduced survival after ALPPS. We could not determine that advanced primary tumor status was an independent risk factor in the LIGRO trial. Rectal tumors were analyzed separately in our study and were found to be a positive prognostic factor, in line with the findings of previous studies,[24,26,27] whereas Petrowsky et al[22] grouped rectal tumors with left-sided colon tumors. The strongest predictor for poor long-term survival found by Petrowsky et al[22] was morphological response to neoadjuvant chemotherapy. However, this difference was not significant in our analysis, though the LIGRO study did not include patients with progressive disease receiving neoadjuvant chemotherapy. Notably, all but 2 long-term survivors in our study experienced regression after receiving neoadjuvant chemotherapy. A higher overall response rate to first-line chemotherapy has been described as a positive prognostic factor for long-term survival.[24]

This study has several limitations that need to be recognized. The LIGRO trial was not designed to explore long-term survival as the primary outcome and the small number of long-term survivors limits the analysis in regard to possible superiority or

noninferiority. The multicenter nature of this study limits the standardization of numerous factors but might increase the generalizability of the results. Surgical techniques may differ between participating centers, and the option of rescue ALPPS limits a clear-cut comparison between the 2 groups.

As discussed in the article by Hasselgren et al.,[18] both TSH and ALPSS are invasive procedures with high morbidity and mortality, and less-invasive treatment options should be sought. Indeed, other treatment options have evolved since the LIGRO trial. Enhanced one-stage ultrasound-guided hepatectomy has been proven to be feasible, with lower morbidity than ALPPS.[28] Minimally invasive ALPPS has also been introduced, but evidence in this regard is limited.[29] One might speculate that a reduction in surgical trauma would lead to fewer complications and lower morbidity, but this is still unknown. Other less-invasive treatment options have emerged, such as PVE combined with hepatic vein embolization (HVE), as described by Guiu et al.[30] The work by Heil et al. in the DRAGON collaborative group showed greater hypertrophy and a greater resection rate for PVE/HVE than for PVE alone, with comparable morbidity and 90-day mortality.[31] Based on unpublished data, this was confirmed in the DRAGON 1 trial, which showed PVE/HVE to be a safe procedure with a high kinetic growth rate and a high resection rate.[32] With less-invasive procedures, it may be possible to reduce the trauma of the first intervention and thereby increase the number of patients suitable for radical hepatectomy. For these reasons, ALPPS may be considered a rescue option if insufficient growth of the FLR is found after PVH/HVE.

CONCLUSIONS

The LIGRO trial revealed greater resectability with ALPPS than with TSH. Extrahepatic disease and a larger CRLM size are negative prognostic factors for long-term survival, whereas tumor-free status in the liver at first follow-up and a rectal primary tumor are positive prognostic factors. Survival did not significantly differ between the patients who underwent resection via ALPPS or TSH.

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