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Health Economic Evaluation of Patients With Colorectal Liver Metastases Randomized to ALPPS or TSH

Analysis From the LIGRO Trial

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Objective: This is a preplanned, health economic evaluation from the LIGRO trial. One hundred patients with colorectal liver metastases (CRLM) and standardized future liver remnant <30% were randomized to associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) or two-staged hepatectomy (TSH).

Summary Background Data: TSH, is an established method in advanced CRLM. ALPPS has emerged providing improved resection rate and survival. The health care costs and health outcomes, combining health-related quality of life (HRQoL) and survival into quality-adjusted life years (QALYs), of ALPPS and TSH have not previously been evaluated and compared.

Methods: Costs and QALYs were compared from treatment start up to 2 years. Costs are estimated from resource use, including all surgical interventions, length of stay after interventions, diagnostic procedures and chemotherapy, and applying Swedish unit costs. QALYs were estimated by combining survival and HRQoL data, the latter being assessed with EQ-5D 3L. Estimated costs and QALYs for each treatment strategy were combined into an incremental cost-effectiveness ratio (ICER). Nonparametric bootstrapping was used to assess the joint distribution of incremental costs and QALYs.

Results: The mean cost difference between ALPPS and TSH was 12,662€, [95% confidence interval (CI): −10,728–36,051; *P* = 0.283]. Corresponding mean difference in life years and QALYs was 0.1296 (95% CI: −0.12–0.38; *P* = 0.314) and 0.1285 (95% CI: −0.11–0.36; *P* = 0.28), respectively. The ICER was 93,186 and 92,414 for QALYs and life years as outcomes, respectively.

Conclusions: Based on the 2-year data, the cost-effectiveness of ALPPS is uncertain. Further research, exploring cost and health outcomes beyond 2 years is needed.

Keywords: associating liver partition and portal vein ligation for staged hepatectomy, colorectal liver metastases, health economic evaluation, two-staged hepatectomy

INTRODUCTION

Colorectal cancer is 1 of the most common malignant tumors.[1] Up to 50% of patients will at some point be affected by metastases, and liver metastases are the most common.[2] Radical resection of liver metastases is a treatment that can lead to long-term survival.[3,4] The majority of patients are not assessed as resectable, often due to the low volume of the future liver remnant (FLR). They can be treated with downsizing chemotherapy and/or techniques to increase the volume of the FLR.[5–7] Two-stage hepatectomy (TSH), with portal vein occlusion followed by hepatectomy, is an established method.[8] Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a newer technique and has a higher resection rate than TSH without an increase in postoperative complications, and improved survival.[9,10] When determining which treatment approaches to prioritize in a healthcare system with scarce resources, both healthcare costs and health outcomes must be considered.

In a health economic evaluation, the health outcomes and costs of relevant treatment strategies are estimated and compared. Health outcome measures often include a combination of patients' perceived health-related quality of life (HRQoL) and survival in quality-adjusted life years (QALYs).[11] The quality component is often measured using generic, nondisease-specific questionnaires, such as EuroQol (EQ-5D). The questionnaire EQ-5D covers the dimensions mobility, self-care, usual activities,

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pain/discomfort, and anxiety/depression.[12] In health economic analysis and studies, the concept "cost" is applied to the cost of the resource, expressed in monetary terms. The concept "resource use" is applied to the use of physical resources, for example, the number of computed tomography (CT) scans.[13]

In the immediate postoperative period, the HRQoL of patients treated with liver resection is reduced compared to preoperative estimation and within 3 months postoperatively, quality of life (QoL) tends to improve, and after 6 months, it is restored to the baseline level in patients treated with liver resection, ranging from wedge resections to hemihepatectomies.[14] For patients treated with ALPPS or TSH, no previous studies have reported the effect of the procedure on HRQoL in the immediate postoperative period. Approximately 2 years after ALPPS, HRQoL is comparable with QoL for the general population.[15]

No previous study has investigated the healthcare costs of ALPPS and TSH in patients with colorectal liver metastases (CRLM).

Regarding the cost-effectiveness assessment, resection has been compared to palliative treatment, including chemotherapy, and has been shown to improve survival and be cost-effective.[16,17] If postoperative chemotherapy were included in the resection group, the cost may not differ between the groups.

The aim of this study is to estimate and compare healthcare costs and HRQoL after treatment with ALPPS and TSH in the settings of advanced CRLM.

MATERIAL AND METHODS

Study Design

This study is a preplanned health economic evaluation from the LIGRO trial (ClinicalTrials.gov, NCT02215577). A detailed description of the study design, including inclusion and exclusion criteria, estimates of the liver volume and surgical procedures and the clinical outcomes, has previously been published.[9,10]

In brief, 100 patients with CRLM and standardized FLR (sFLR) below 30% were randomized to ALPPS or TSH. The sFLR was the percentage of the estimated total liver volume. Estimated total liver volume was calculated based on the formula according to Mosteller.[18]

The inclusion criteria were CRLM, sFLR <30% and the ability to undergo resection with a TSH approach. The exclusion criteria were age below 18 years and severe comorbidity. Severe comorbidity was defined as significant comorbidity rendering the patient unsuitable for major liver surgery and which resulted in the patient being classified as American Society of Anesthesiologist IV. Patients were included after preoperative chemotherapy and with either stable disease or regression. Patients were randomized in a 1:1 manner. Those randomized to TSH were either treated with portal vein embolization (PVE) or portal vein ligation (PVL) at the discretion at each center. For patients randomized to ALPPS, the first intervention consisted of ligation of the portal vein to the lobe to be resected and transection of the parenchyma. During the second intervention, the deportalized lobe was resected. For patients in both groups, metastases in the FLR were either resected with wedge resection or treated with ablation.

Ethical approval was obtained in all participating countries.

Follow-Up

The total follow-up time was at least 2 years for every patient. The patients had their first postoperative follow-up approximately 4 weeks after discharge and then after 4, 8, 12, 18, and 24 months. After 24 months, patients were followed according to clinical routine, and therefore, data beyond 2 years were not included in this analysis. At each follow-up, either CT or magnetic resonance imaging (MRI) was performed. At each follow-up, it was noted if the patient was assessed as tumor-free, had recurrent disease or residual tumor. For patients with recurrent disease, resection or palliative chemotherapy were considered. The first patient was included in 2014, and the last was included in 2016.

Economic Evaluation

Comparisons of resource use, costs, and health outcomes were performed for all included patients. The analysis time started at the first intervention and continued 2 years onward or until death. Cost-effectiveness analyses were performed by relating incremental healthcare costs to incremental health outcomes of ALPPS compared with TSH in incremental cost-effectiveness ratios (ICERs). The reported ICERs should be interpreted as the additional cost of achieving an additional health outcome if ALPPS is applied rather than TSH.[19]

Data Presentation

Costs were evaluated in 3 time periods. The perioperative period (period 1) includes all costs from the first intervention until 30 days after the final intervention in the liver. This includes all liver surgical interventions, any postoperative complications and readmissions. The second period (period 2) starts after the perioperative period and continues up to 12 months. Period 3 starts at 13 months and continues until 24 months.

Resource Use

All surgical interventions were included, as was the length of stay after the interventions. During the follow-up, diagnostic procedures and chemotherapy were included.

Interventions

The interventions in the trial were in the ALPPS group intervention 1 and intervention 2 and in the TSH group PVE, PVL, radical hepatectomy and crossover to ALPPS interventions 1 and 2. For patients randomized to TSH and treated with crossover ALPPS, the costs and resource use for the entire ALPPS procedure were included in intervention 2. Any postoperative complication ≥3a according to the Clavien-Dindo classification was included.[20] Resection of the primary tumor, resection/ablation of recurrent disease in the liver and resection of extrahepatic disease (EHD) were registered.

Hospitalizations

The length of stay after the ALPPS and TSH interventions were registered, and the length of stay for those patients who were readmitted due to postoperative complications within 30 days. Hospitalization for those patients who underwent resection of the primary tumor and/or EHD/recurrent disease was also recorded in the trial, although not the length of stay. In the analysis, the length of stay of the respective procedure was based on the mean length of stay at Linköping University Hospital. The number of patients requiring care at the intensive care unit was recorded.

Diagnostic Procedures

The number of radiological examinations and whether CT or MRI was performed were recorded. It was assumed that the patient had a CT thorax at each CT/MRI of the abdomen.

Chemotherapy

The type of chemotherapy and the number of cycles were noted. For patients for whom the number of cycles of chemotherapy was missing, it was replaced with the mean number of cycles for the patients undergoing either ALPPS or TSH, depending on the patient's group allocation.

Unit Costs

To arrive at a healthcare cost per patient in the trial, resource use was multiplied by unit costs. These are reported in Table 1.

Interventions

The unit costs of all surgical procedures were based on the mean operating time at Linköping University Hospital for the respective procedures. Included in the cost of surgical procedures were the preoperative preparation, operating time, surgical equipment, recovery at the postoperative ward, anesthesiologist, nurses and surgeons.

Hospitalization

To estimate the unit cost of hospitalization, the cost of care in each ward category was based on the number of days in the respective ward. Data regarding the length of stay at the intensive care unit was missing for some patients and was imputed with the mean length of stay at the intensive care unit. Data regarding the length of stay after resection of the primary tumor and EHD was missing and was replaced with the mean length of stay after the respective procedure at Linköping University Hospital.

TABLE 1.
Unit Costs

Resource	Unit Costs (EUR)
Intervention 1	
ALPPS intervention 1	6694
PVE	5349
PVL	6903
Ablation of metastases in the FLR, performed in conjunction with ALPPS intervention 1 or TSH	2125
Resection of metastases in the FLR, performed in conjunction with ALPPS intervention 1	327
Resection of metastases in the FLR, performed in conjunction with PVE	6159
Resection of metastases in the FLR, performed in conjunction with PVL	327
Intervention 2	
ALPPS intervention 2	6170
Ablation of metastases in the FLR, performed in conjunction with ALPPS intervention 2 or TSH	2125
Radical hepatectomy for patients randomized to TSH	7266
Explorative laparotomy	3488
Crossover, ALPPS intervention 1	6694
Crossover, ALPPS intervention 2	6627
Microscopic histopathological examination	
Wedge resection	164
Right/extended right hemihepatectomy	348
Hospitalization	
Surgical ward, administration cost for each care event	1867
Surgical ward, daily cost	420
Intensive care unit, administration cost for each care event	3081
Intensive care unit, daily cost	7563
Diagnostic procedure	
Computed tomography (thorax and abdomen) and visit to the outpatient clinic	545
Magnetic resonance imaging abdomen and computed tomography thorax and visit to the outpatient clinic	874
Chemotherapy	
5FU	317
Irinotecan	81
Oxaliplatin	186
Capecitabine	51
Bevacizumab	210
Cetuximab	3711
Panitumumab	3640

5FU indicates fluorouracil; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; PVE, portal vein embolization; PVL, portal vein ligation; TSH, two-staged hepatectomy.

Diagnostic Procedures

The cost of radiological examinations and visits to the outpatient clinic was calculated based on the number and types of examinations and costs at Linköping University Hospital.

Chemotherapy

The cost of oncological treatment was calculated according to the cost of the respective oncological agent and the number of cycles.

All calculated and estimated costs are the costs at Linköping University Hospital in Sweden in 2018. The conversion to the euro was based on the exchange rate set by the Swedish National Bank in October 2018 (1 EUR = 10.71 SEK).

Health Outcomes

For the assessment of QoL, the EQ-5D-3L was used. The EQ-5D covers 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, from no symptoms/problems to severe symptoms/problems. The EQ-5D has been validated for translation to the Scandinavian languages.[21]

The EQ-5D was answered at inclusion, then 4 weeks after the second intervention, and then after 6, 12, and 24 months. All randomized patients answered the EQ-5D before intervention 1. Only patients who completed both interventions were followed up with the EQ-5D.

To obtain a single value for each health state, the United Kingdom EQ-5D index tariff was used.[22] To calculate QALYs, the area under the curve was calculated, and it was assumed that the transition of health states between measurement points followed a straight line. The starting point was the date of intervention 1. Deceased patients were assigned an HRQoL of zero for the remaining measurements.

Statistical Analysis

All analyses were performed according to the intention-to-treat principle. The results are expressed as the mean 95% confidence interval (CI). Continuous data were compared using *t* tests, and categorical data were compared using χ^2. A $P < 0.05$ was considered statistically significant. Nonparametric bootstrapping was performed to display the joint distribution of the mean incremental costs and QALYs in respective life years (LYs). Nonparametric bootstrapping was used because it does not make any assumption about the distribution of the observations.[23]

Analyses were performed using IBM SPSS (version 25; IBM Corp, Armonk, NY).

RESULTS

Fifty patients were randomized to ALPPS and 50 to TSH. Two patients randomized to ALPPS and 1 patient randomized to TSH were excluded due to incorrect initial inclusion (severe comorbidity, sFLR >30%) or progressive disease. There was no significant difference between the groups regarding baseline characteristics (Table 2).

TABLE 2.

Preoperative Clinical Data

	ALPPS (n = 48)	TSH (n = 49)	P
Age (years) at the diagnosis of CRLM	64 ± 9	63 ± 12	0.68
Gender (male/female)	32/16	36/13	0.46
Synchronous/metachronous	38/10	44/5	0.148
Primary tumor rectum/right colon/left colon	16/11/16	14/10/18	0.729
Number of liver metastases	8 ± 4	8 ± 5	0.48
Size of the largest liver metastasis (mm)	56 ± 42	49 ± 39	0.405
Number of patients with metastases in the FLR on preoperative CT/MRI	29 (60%)	30 (63%)	0.84
Primary tumor resected at inclusion (yes/no)	29/19	31/18	0.77
EHD	11*	7	0.59
Response to chemotherapy (stable disease/regression)	9/38	10/38	0.80

Clinical data for included patients.

*Including 2 patients who had lung metastases resected before inclusion in the trial.

CRLM indicates colorectal liver metastases; EHD, extrahepatic disease.

Cost and Resource Use Period 1

All patients underwent the first intervention and there was no significant difference regarding the cost of the first surgical procedure. The mean cost of PVE was higher than the mean cost of ALPPS intervention 1. Some patients treated with PVE had local resection of metastases in the FLR, which additionally added to the cost and resource use. There were no differences in cost when the length of stay and number of radiology exams were included ($P = 0.388$) (Table 3).

Forty-five patients randomized to ALPPS underwent the second intervention. Forty patients randomized to TSH were included in the cost analysis of the second intervention. Thirty-nine underwent right or extended right hemihepatectomy, including 12 patients resected after crossover to ALPPS. The procedural

TABLE 3.

Cost for Interventions Undertaken During Period 1, Period 2 and Period 3, for Patients Randomized to ALPPS Respective TSH

	ALPPS	TSH	P	Mean Difference
Period 1				
Intervention 1, number of patients	48	49		
Cost, surgical procedure and care at the recovery ward	7714 (7501–7926)	7566 (6906–8226)	0.671	148
Total cost intervention 1	11,685 (11,305–12,064)	12,269 (10,981–13,557)	0.388	–584
Intervention 2, number of patients	45*	40†		
Cost, surgical procedure and care at the recovery ward	7114 (6830–7397)	9882 (8799–10,966)	<0.001	–2769
Total cost, intervention 2	17,973 (16,015–19,930)	22,367 (17,266–27,467)	0.096	–4394
Total cost, intervention 1 and 2‡	29,017 (26,729–31,305)	31,388 (26,238–36,538)	0.403	–2371
Postoperative complications 3a–3b number of patients	16	15		
Cost, postoperative complications	1480 (653–2307)	797 (220–1373)	0.163	684
Care at the intensive care unit, number of patients	5	5		
Cost, intensive care unit	18,207	18,207		0
Readmitted, number of patients	10	12		
Cost, readmitted	9388 (3554–15,223)	5835 (4182–7487)	0.168	3554
Total cost, period 1	54,311 (36,224–72,398)	50,222 (38,510–61,935)	0.702	4089
Period 2				
Number of patients§	47	48		
Resection of primary tumor (13/10)	8202 (7776–8629)	8527 (8057–8997)	0.273	–325
Resection EHD (8/9)	9715 (8357–11,073)	9701 (6601–12,796)	0.993	14
Diagnostic procedure (42/38)	1806 (1653–1959)	1405 (1214–1596)	0.001	401
Chemotherapy (28/27)	18,431 (9811–27,051)	10,922 (4269–17,575)	0.165	7509
Total cost, period 2‖	18,053 (11,950–24,156)	12,114 (7247–16,980)	0.128	5940
Period 3				
Number of patients¶	40	36	0.325	
Resection EHD (4/4)	7284 (4080–10,489)	10,287 (3110–17,463)	0.270	–3002
Diagnostic procedures (32/27)	982 (817–1146)	1201 (1021–1382)	0.071	–220
Chemotherapy (10/5)	27,768 (13,679–41,857)	24,637 (585–48,690)	0.775	3131
Total cost, period 3	10,249 (4284–16,215)	7028 (4886–12,655)	0.413	3222
Total cost, period 1–3	77,530 (58,602–96,459)	64,868 (50,654–79,082)	0.283	12,662
Number of patients alive at end of period 3	35	23	0.021	

All costs are expressed as the mean (95% CI) and in EUR.

*Including 1 patient resected in violation of protocol.

†Including 12 patients treated with crossover to rescue ALPPS and 1 patient with carcinomatosis at explorative laparotomy.

‡Including the cost of the surgical procedures, care at the recovery ward, care at the surgical ward and the microscopic histopathological examination.

§Number of patients alive at approximately 4 weeks after discharge after the last intervention, including patients not proceeding to intervention 2.

‖Excluding costs for intervention 1 and intervention 2 and the first 30 days after discharge from intervention 2.

¶Number of patients alive at the start of periods 2 and 3, respectively. EHD, extrahepatic disease. Data regarding the length of stay at the intensive care unit was missing for some patients and was imputed with the mean length of stay at the intensive care unit. Data regarding the length of stay after resection of the primary tumor and EHD was missing and was replaced with the mean length of stay after the respective procedure at the Linköping University Hospital.

cost for intervention 2 was significantly higher for patients randomized to TSH ($P < 0.01$). When the total cost of intervention 2 was calculated, the cost for patients randomized to TSH was still higher compared to the cost for patients randomized to ALPPS, although the difference did not reach statistical significance (P = 0.096). The combined cost of intervention 1 and intervention 2 did not differ between ALPPS and TSH (P = 0.403).

Ten patients randomized to ALPPS were readmitted, compared to 12 patients randomized to TSH. The cost of readmission did not differ significantly between the groups (P = 0.168) (Table 3).

Period 2

At the start of period 2, 47 patients randomized to ALPPS were alive and 48 patients randomized to TSH. Nineteen (40%) and 18 (37%) patients randomized to ALPPS and TSH, respectively, had not had the primary tumor resected before inclusion (P = 0.77). Thirteen (27%) and 10 (20%) patients, respectively, had resection of the primary tumor (P = 0.80).

Twenty-eight (58%) and 27 (56%) patients randomized to ALPPS and TSH, respectively, were treated with chemotherapy, and there was no significant difference in the associated costs.

Twenty-four (50%) of the 32 patients (65%) randomized to ALPPS and TSH, respectively, had recurrent disease during period 2 (P = 0.093). Eight (33%) and 9 (28%) patients were treated with ablation or resection, respectively. Two (6%) patients randomized to TSH underwent resection of EHD and ablation of recurrent disease in the liver. The difference in resection of recurrent disease did not reach statistical significance (P = 0.218).

The total cost and resource use during period 2 did not differ significantly (P = 0.128). For a detailed description of costs and resource use, see Table 3.

Period 3

At the start of period 3, 40 (83%) patients randomized to ALPPS and 36 (73%) patients randomized to TSH were alive (P = 0.325). Nine in each group were assessed as tumor-free (23% and 25%; P = 0.665). Four (13%) and 4 (15%) patients with recurrent disease in the liver were treated with ablation or resection, respectively (P = 0.80). Ten (25%) and 5 (14%) patients randomized to ALPPS and TSH, respectively, were treated with chemotherapy (P = 0.775). No significant difference regarding cost and resource use was found (P = 0.413) (Table 3).

Sum of Costs and Resource Use From Intervention 1 to the End of Period 3

The total cost was 54,311 EUR (95% CI: 36,224–72,398) for ALPPS and 50,222 EUR (95% CI: 38,510–61,935) for TSH, including length of stay, readmissions and postoperative complications (P = 0.702). The total cost for period 2 was 18,053 EUR (95% CI: 11,950–24,156) for ALPPS and 12,114 EUR (95% CI: 7247–16,980) for TSH (P = 0.128). The cost for period 3 was 10,249 (95% CI: 4284–16,215) for ALPPS and 7028 (95% CI: 1973–12,082) for TSH (P = 0.413).

Health Outcomes

The EQ-5D completion rate was the highest before intervention 1; 85% for patients randomized to ALPPS and 90% for patients randomized to TSH. The completion rate declined and was the lowest at 24 months. The adjusted QoL at inclusion and after approximately 1, 6, 12, and 24 months is shown in Figure 1. In both groups, the adjusted QoL declined over time.

The mean quality-adjusted survival was 1.25 (95% CI: 1.08–1.42) for patients randomized to ALPPS and 1.11 (95% CI: 0.94–1.27) for patients randomized to TSH (P = 0.234).

The mean number of life years was 1.68 (95% CI: 1.5–1.87) for patients randomized to ALPPS and 1.55 (95% CI: 1.37–1.73) for patients randomized to TSH (P = 0.314).

Cost-Effectiveness

The cost-effectiveness analysis revealed that the mean cost difference between ALPPS and TSH was 12,662 EUR (95% CI: −10,728–36,051; P = 0.283). The mean difference in life years was 0.1296 (95% CI: −0.12–0.38; P = 0.314), and the mean difference in QALYs was 0.1285 (95% CI: −0.11–0.36; P = 0.28). Accordingly, the ICER for life years was 92,414, and the ICER for QALYs was 93,186.

The joint distribution of costs and the respective costs of QALYs and LYs are shown in Figures 2, 3, respectively. Both

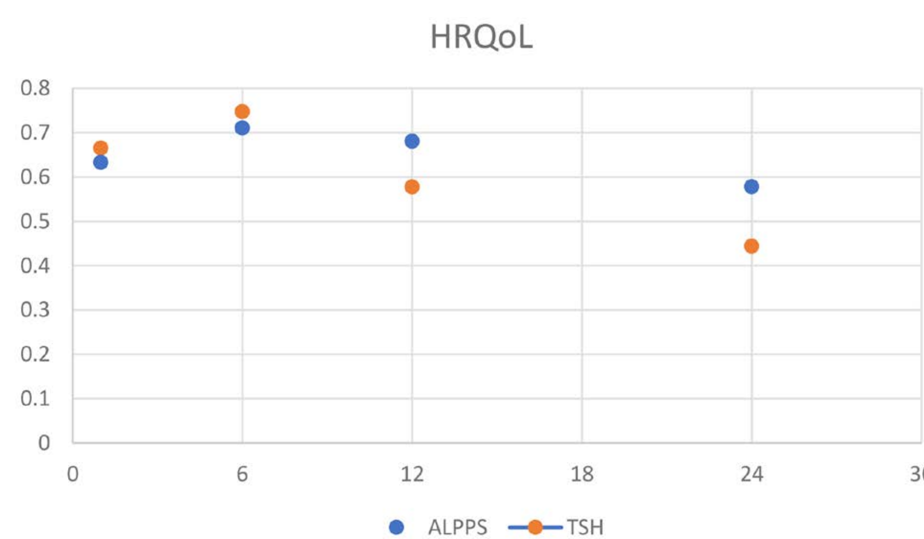

FIGURE 1. HRQoL at inclusion and at approximately 1, 6, 12, and 24 months after intervention 2. All randomized patients were included at all time points; deceased patients were assigned a value of 0 for HRQoL. Missing data are imputed with corresponding values from each cohort. In both groups, HRQoL declined over time. ALPPS indicates associating liver partition and portal vein ligation for staged hepatectomy; HRQoL, health-related quality of life; TSH, two-staged hepatectomy.

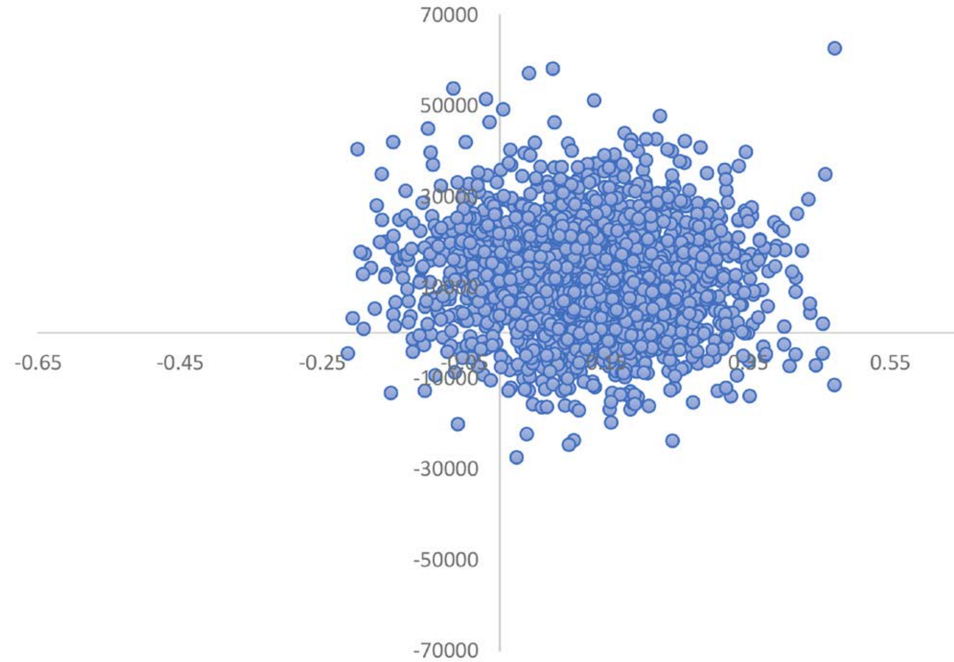

FIGURE 2. Result from the probalistic analysis on the cost-effectiveness plane. The incremental cost and effect, expressed as QALYs, are calculated as ALPPS minus TSH. The figure represents the nonparametric bootstrapping, were 2000 samples were drawn and each dot represent the incremental cost of ALPPS versus TSH divided by the incremental QALYs. The *x* axis represents the incremental cost, and the *y* axis represents the incremental QALY's. ALPPS indicates associating liver partition and portal vein ligation for staged hepatectomy; QALY, quality-adjusted life years; TSH, two-staged hepatectomy.

analyses indicate that ALPPS is more costly but also more effective. The figures illustrate the results from the probalistic analysis on the cost-effectiveness plane. The *x* axis represents the incremental cost, and the *y* axis represents the incremental QALY´s respective LYs.

DISCUSSION

This is the first health economic evaluation of patients with advanced CRLM randomized to ALPPS or TSH. The only treatment with the potential to achieve long-term survival is resection. For patients with advanced CRLM and often bilobar disease, resection is often achieved with a 2-stage approach. The results from this study indicate that there is no significant difference in resource use and costs or any difference in QALYs or LYs for patients randomized to ALPPS or TSH. However, the study period is relatively short. A longer study period may not show the same results, because the survival of patients randomized to ALPPS is significantly longer than the survival of patients randomized to TSH.[10]

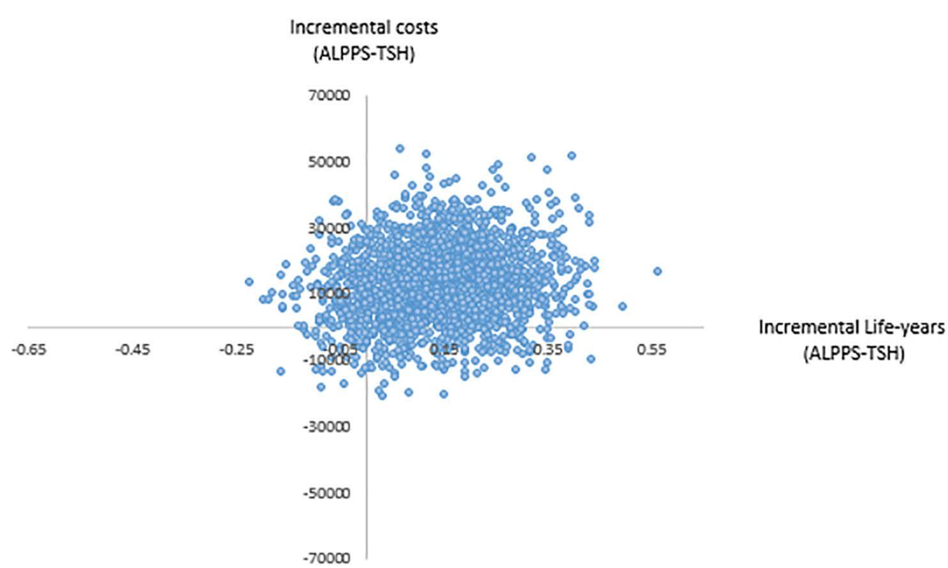

FIGURE 3. Result from the probalistic analysis on the cost-effectiveness plane. The incremental cost and effect, expressed as life years, are calculated as ALPPS minus TSH. The figure represents the nonparametric bootstrapping, were 2000 samples were drawn and each dot represent the incremental cost of ALPPS versus TSH divided by the incremental LYs. The *x* axis represents the incremental cost, and the *y* axis represents the incremental QALY's. ALPPS indicates associating liver partition and portal vein ligation for staged hepatectomy; TSH, two-staged hepatectomy.

The mean total cost was 77,530 EUR for each patient randomized to ALPPS and 64,868 EUR for patients randomized to TSH (P = 0.283). The mean annual cost per randomized patient was 38,765 EUR and 32,434 EUR, respectively. One must take into consideration that a significantly higher proportion of patients randomized to ALPPS were alive at the end of this study compared to the number of patients randomized to TSH.

Because the cost was higher for patients randomized to ALPPS and no significant difference in QALYs or LYs was found, it is difficult to draw a firm conclusion regarding which approach is most cost-effective. However, it cannot be excluded that if patients treated with rescue ALPPS were analyzed as a separate group, the result would be different.

Further analysis of costs and resource use demonstrates differences between the groups. The total cost of interventions 1 and 2 was higher for patients randomized to TSH. To a large extent, this can be explained by the additional cost for patients treated with rescue ALPPS.

The mean cost during periods 2 and 3 was higher for patients randomized to ALPPS. This is largely explained by the higher chemotherapy cost for patients randomized to ALPPS. A higher proportion of patients randomized to ALPPS were administered monoclonal antibodies in addition to chemotherapy. During period 2, 43% of patients randomized to ALPPS (compared to 26% of patients randomized to TSH) were treated with monoclonal antibodies. Furthermore, a higher proportion of patients randomized to ALPPS with recurrent disease were treated with chemotherapy. This may indicate that a higher proportion of patients randomized to TSH were assessed as not suited for palliative chemotherapy.

Although the applied costs were Swedish, it is reasonable to assume that the resource use did not differ in the different Scandinavian countries.

In a previous retrospective study in which patients with CRLM treated with ALPPS were compared to those treated with palliative chemotherapy, no significant difference in survival was shown.[24] The authors argued that palliative chemotherapy therefore may be an alternative to ALPPS. However, the survival for patients in that study was considerably lower than the survival for patients in the current study.[10] In a previous study, the results of which were based on a decision model, liver resection was found to be cost-effective compared to chemotherapy.[25] However, prospective studies are lacking.

This study has some limitations that must be acknowledged. First, the sample size in the LIGRO trial was not calculated to detect a difference in costs; the power calculation was performed to detect a difference in resection rate. Furthermore, data regarding some resource use are lacking, and some assumptions have been made. For example, the assumption that were made about the length of stay at the intensive care unit. The number of patients did not differ, but it is possible that the length of stay did, and therefore the cost. However, an analysis without the assumptions stated in the Material and Methods section was made (data not shown). Although the costs differed, there still was no significant difference for patients randomized to ALPPS compared to TSH.

Another limitation is that some unit costs are not included in this study, for example, home care.[26] It is reasonable to assume that the cost per patient would not differ and that more patients randomized to TSH received palliative care, which would likely increase the mean cost for the TSH group and thereby reduce the observed difference in cost between the groups.

Regarding HRQoL, the results must be interpreted with caution due to the declining response rate over time. Furthermore, only patients who did proceed through intervention 2 responded to the questionnaire. The imputation performed in this study and the subsequent results are supported in a previous study, in which it was found that patients with CRLM who underwent noncurative surgery had lower HRQoL than patients treated with resection.[27]

CONCLUSIONS

Based on the 2-year data, no significant difference in cost-effectiveness could be found between ALPPS and TSH. Further research exploring the costs and health outcomes beyond 2 years is needed. However, 1 should bear in mind that the resection rate was higher for patients randomized to ALPPS.

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