World J Surg (2019) 43:2281–2289
https://doi.org/10.1007/s00268-019-05031-w

ORIGINAL SCIENTIFIC REPORT

Long-Term Outcome After Conventional Two-Stage Hepatectomy Versus Tourniquet-ALPPS in Colorectal Liver Metastases: A Propensity Score Matching Analysis

Ricardo Robles-Campos[1,4] · Roberto Brusadin[1] · Asunción López-Conesa[1] · Víctor López-López[1] · Álvaro Navarro-Barrios[1] · José J. López-Espín[2] · Julio Arévalo-Pérez[3] · Pascual Parrilla[1]

Published online: 22 May 2019

Abstract

Background To compare the overall survival (OS) and disease-free survival (DFS) of Tourniquet-ALPPS (T-ALPPS) and conventional two-stage hepatectomy (TSH) in patients with colorectal liver metastases (CRLM).

Methods A retrospective study from a prospectively collected database was performed between October 2000 and July 2016. TSH was performed before September 2011, after which time T-ALPPS became the technique of choice. A propensity score matching (PSM) was performed based on a 1:1 ratio with consideration of the following variables: number and size of metastases, bilobar disease presence, and chemotherapy received.

Results Thirty-four patients received T-ALPPS; 41 patients received TSH. After PSM, 21 patients remained in each group, with 100% resectability in the T-ALPPS group and 90.5% resectability in the TSH group. The median OS for TSH was 41 months; for T-ALPPS, the median OS was 36 months ($P = 0.925$). The median DFS was 16 months in the TSH group; the median DFS was 9 months in the T-ALPPS group ($P = 0.930$). The 1-, 3-, and 5-year OS for TSH was 81%, 66.7%, and 23.8% vs. 76.2%, 57.1%, and 22.9% for T-ALPPS, respectively. The 1-, 3-, and 5-year DFS for TSH was 66.7%, 9.5%, and 5% vs. 44.6%, 11.1%, and 11.1% for T-ALPPS, respectively. The volume increase with T-ALPPS was superior to that with TSH (68% vs. 39%; $P = 0.018$). There were no differences in morbidity and mortality after stages 1 and 2.

Conclusions T-ALPPS produces a similar outcome to TSH, indicating that it could be a safe and effective alternative for curative hepatectomy for all patients.

Introduction

Liver resection offers a chance of cure for patients with colorectal liver metastases (CRLM) [1, 2]. Only 15–30% of patients are initially candidates for surgery [1]. In this setting, a multidisciplinary strategy that includes new chemotherapeutic agents has enabled resection for a remarkable percentage of patients [3, 4].

Liver regeneration techniques have also increased the number of patients who are suitable for surgery, since hypertrophy that occurs in the future liver remnant (FLR) could prevent post-hepatectomy liver failure (PHLF). The first hypertrophy technique was portal vein embolization (PVE) [5]; René Adam et al. [6] later introduced the two-

✉ Ricardo Robles-Campos
rirocam@um.es

1 Department of Liver Surgery and Transplantation, Virgen de La Arrixaca Clinic, University Hospital, IMIB-Arrixaca, Murcia, Spain

2 Miguel Hernandez University, Elche, Alicante, Spain

3 Radiology Department, Memorial Sloan Kettering Cancer Center, New York, USA

4 Department of Surgery, Virgen de La Arrixaca Clinic, University Hospital, El Palmar, Murcia, Spain

stage hepatectomy (TSH). Both techniques are used in patients with large unilobar or multiple bilobar liver metastases with insufficient FLRs. The volume increase achieved with PVE or TSH does not exceed 50% in most series. In addition, they require a prolonged regeneration time (between 4 and 16 weeks) that has been associated with a dropout rate of 30%, which is mainly due to tumor progression [7–9].

Recently, a new surgical technique known as associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) achieves an increase in FLR of 60–80% in only 9 days, mainly by interrupting intrahepatic vascular collaterals using parenchyma bipartition in the first stage [10]. Although ALPPS resectability is greater than 90%, long-term outcomes for CRLM are contradictory [11–16]. Only one prospective study comparing ALPPS with TSH has been published (LIGRO trial) [17], but it focused on postoperative surgical outcomes. Only recently, a translational substudy of that trial focusing on early recurrence has been published [18]. Due to the high initial morbidity and mortality of ALPPS [10, 19, 20], we developed a modification for the technique by placing a tourniquet on the hepatic bipartition line during stage 1 (ALTPS or Tourniquet-ALPPS) in order to avoid liver partition and minimize the risk associated with the first intervention [21].

The aim of the present study was to compare the results of Tourniquet-ALPPS (T-ALPPS) and TSH in CRLM, with the primary end-point of analyzing the overall survival (OS) and disease-free survival (DFS) at the 1-, 3-, and 5-year follow-up.

Patients and methods

Study design

We performed our first two-stage liver resections in October 2000 and collected the data in a prospective database [22]. Two types of surgical techniques were consecutively carried out: conventional TSH initially and T-ALPPS later. We performed a retrospective study between October 2000 and July 2016 comparing these surgical techniques in patients with CRLM. In all cases, preoperative assessments consisted of tumor markers (CEA, Ca 19.9), CT, or MRI and PET-CT. All patients were informed about the risks of the procedure and signed an informed consent.

Inclusion and exclusion criteria

Patients with liver metastases, an insufficient FLR, and who required a two-stage liver resection were included. Limited extrahepatic disease (i.e., few lung metastases or a single peritoneal node) was not a contraindication for surgery if there was a favorable response to neoadjuvant chemotherapy and an R-0 could be reached. The exclusion criteria we used were the presence of extensive extrahepatic disease, non-response to chemotherapy, and a poor general status that contraindicated surgery (ECOG > 2).

Propensity score matching

Considering that the two techniques were used in two different periods of time, we attempted to avoid bias relating to changes in chemotherapy or surgical indications (i.e., ALPPS was used in some cases with large unilobar disease and a very small FLR) by performing a propensity score matching (PSM). The two-stage group was matched at a 1:1 ratio with the T-ALPPS group with respect to the following variables: number and size of the metastasis, the presence of bilobar disease, and the type of chemotherapy used.

Outcome measures

The primary end-points were OS and DFS at 1, 3, and 5 years; these end-point times were calculated from the date of stage 1 (all patients had at least 2 years of follow-up). Secondary end-points were morbidity (global and $\geq$ IIIB) [23] and mortality after stages 1 and 2, as well as the increase in FLR after stage 1.

FLR was calculated in mL and percentage using CT scans before both stages. The inter-stage interval was defined as the time period between the first and second surgical operations. FLR was considered insufficient when it was less than 25% in patients with a healthy liver and less than 35% in those who had received chemotherapy. A ratio < 0.5 for volume/bodyweight was considered insufficient in patients without neoadjuvant chemotherapy; a ratio < 0.7 in patients with prior chemotherapy was insufficient. Liver failure was defined using the International Study Group of Liver Surgery criteria [24].

Surgical technique

Two-stage hepatectomy

In stage 1 after removing the metastases of the FLR, portal occlusion was performed intraoperatively by PVL. The first CT scan was performed two weeks after surgery and repeated every week until a sufficient FLR was reached. In stage 2, a major liver resection was performed. In 4 patients, the first intervention was performed using a laparoscopic approach; the second stage was completed by laparoscopy in 2 of them (right hepatectomy in both cases).

Tourniquet-ALPPS

The technical details of T-ALPPS have been previously described [21]. In stage 1, after removing the metastases of the FLR, the right portal vein was sectioned. We placed a tourniquet in the parenchymal section line to avoid complete division of the liver; then, we knotted the tourniquet tightly enough to completely occlude the intrahepatic circulation.

The tourniquet was inserted on the Cantlie line or umbilical fissure depending on the hepatectomy to be performed in the second intervention. On the 7th postoperative day, volumetric CT was performed. During stage 2, the tourniquet could be used to perform the hanging maneuver, and the liver bipartition was performed following the ischemic line produced by the tourniquet.

Chemotherapy and follow-up

Patients were discussed in a weekly multidisciplinary committee. Neoadjuvant chemotherapy was administered normally, and a first re-evaluation was performed after 6 cycles. In the case of response according to RECIST [25] criteria, surgery was performed; otherwise, chemotherapy was continued until an adequate response was obtained. Chemotherapy between the two stages was indicated in TSH patients when disease progression was detected. In patients who underwent T-ALPPS, no inter-stage chemotherapy was usually indicated, given the few days that elapsed between the two interventions. Adjuvant chemotherapy was administered in all cases after completion of the two stages. Follow-up was performed with CT and tumor markers every 3 months during the first year and every 4–6 months from the second year.

Statistical analysis

We performed a 1:1 propensity score matching between the T-ALPPS group and the TSH group using a logistic regression with a match tolerance of 0.1. We included the following variables: number and size of metastases, presence of bilobar disease, and type of chemotherapy used.

Variables with continuous values are reported as medians with accompanying ranges and were compared using the Mann–Whitney *U* test. Variables with categorical values were compared using the Chi-squared test or Fisher's exact test. OS was calculated from the date of stage 1 until death or the last follow-up, and DFS was calculated from the date of stage 1 until the first recurrence. Survival analysis was performed by intention to treat. OS and DFS curves in both groups were generated using the Kaplan–Meier method and compared with the log-rank test. For all tests, the statistical significance (s.s.) was defined as $P < 0.05$. Statistical analysis was performed with SPSS 19.0 (IBM, Chicago, IL, USA).

Results

Demographic characteristics and results of the global series

Seventy-five patients with CRLM were operated on during the study period: 41 patients with TSH before September 2011 and 34 patients with T-ALPPS from October 2011 to July 2016, with 100% resectability for T-ALPPS and 92.7% for TSH. In Table 1, we summarized the clinicopathological data.

Liver regeneration (volume increase and kinetic growth) was higher and was reached in a shorter time with T-ALPPS than with TSH. Serious morbidity and mortality rates were similar in both groups (Table 2).

The 1-, 3-, and 5-year OS for TSH was 82.9%, 48.8%, and 26.8% vs. 82.4%, 64.7%, and 35.3% for T-ALPPS, respectively ($P = 0.244$). The 1-, 3-, and 5- year DFS for TSH was 61.8%, 15.4%, and 2.6% vs. 54.8%, 12.9%, and 12.9% for T-ALPPS, respectively ($P = 0.822$).

Results after propensity score matching

After PSM, 21 patients were included in each group; there were no differences in the demographic variables or in the oncological characteristics of the patients' primary tumors, liver metastases, or neoadjuvant chemotherapies. Resectability of the TSH group was 90.5% (two patients did not reach the second stage due to tumor progression), whereas resectability was 100% in the T-ALPPS group.

Survival outcome according to intention to treat

The median OS for TSH (including the 2 dropout patients) was 41 months (CI 36.5–45.4); the OS for T-ALPPS was 36 months (CI 10–78.8) ($P = 0.925$). The median DFS in the TSH group was 16 months (CI 12.6–19.3); in the T-ALPPS group, DFS was 9 months (CI 6.2–11.7), which lacked s.s. ($P = 0.930$). The 1-, 3-, and 5-year OS for TSH was 81%, 66.7%, and 23.8% vs. 76.2%, 57.1%, and 22.9% for T-ALPPS, respectively. The 1-, 3-, and 5-year DFS for TSH was 66.7%, 9.5%, and 5% vs. 44.6%, 11.1%, and 11.1% for T-ALPPS, respectively (Figs. 1 and 2).

In the TSH group, 14 patients remained alive for more than 3 years and 4 patients for more than 5 years; in the T-ALPPS group, 7 patients remained alive at 3 years and 6 patients were alive for more than 4 years. Six patients in the TSH group had recurrence within the first year after surgery, two of these recurrences were exclusively in the

Table 1 Demographic and clinical data

Before matching with PS				After matching with PS		
Parameters	TSH (n = 41)	T-ALPPS (n = 34)	p	TSH (21)	T-ALPPS (21)	p
Age, yr (range)	57 (26–74)	64.5 (36–83)	0.021	59 (47–74)	66 (44–83)	0.155
Gender (male)	25	25	0.174	14	15	0.161
ASA						
II	26	15	0.095	12	6	0.061
III	15	19		9	15	
T						
T1–T2	4	3	0.890	2	1	0.549
T3–T4	37	31		19	20	
Nodes						
N0	15	7	0.130	9	3	0.40
N1-2	26	27		12	18	
Synchronous						
	34	24	0.204	17	15	0.469
Primary tumor						
Right colon	9	6	0.096	6	6	0.757
Rest of colon	13	19		10	8	
Rectum	19	9		5	7	
N ° nodules, median (range)	8 (2–14)	4.5 (1–24)	0.026	8 (2–14)	8 (2–24)	0.840
Tumor size (cm), median (range)	3 (2–5)	4 (1–15)	0.03	2.3 (2–5)	3 (1–6)	0.08
CEA ng/ml, median (range)	23 (1–418)	17.5 (1–402)	0.759	18.5 (1–256)	18 (1–285)	0.919
Extrahepatic dis.,	7	6	0.398	5	4	0.278
Lung	6	5		4	3	
Peritoneum	1	1		1	1	
Neoadjuvant Ch	32	29	0.423	21	19	0.147
Oxaliplatino	24	17		15	11	
Irinotecan	5	6		4	3	
Both	3	2		2	2	
Capecitabina + cetuximab	0	4		0	3	
Biological agents	9	11	0.692	7	7	1

liver and could be resected. In the T-ALPPS group, 10 patients had recurrence in the first year, and two of these were exclusively in the liver and could be resected.

Volumetric data

The FLR increase with T-ALPPS was higher (68%; range 21.8–100%), than the increase with TSH (39%; range 21–66%) (P = 0.018). The inter-stage interval in the TSH group was 45 days (range 28–60 days); the inter-stage interval in the T-ALPPS group was 15 days (range 9–31 days) ($P < 0.001$). There was no difference in the ratio of volume/body weight for these two groups, but the kinetic growth was higher in T-ALPPS than in TSH ($P < 0.001$) (Table 2).

Postoperative morbidity and mortality

In stage 1, there were no differences in blood losses, transfusions, or hospital stays. The surgical time was higher in the T-ALPPS group (P = 0.024). Major complications ($\geq$ IIIB) were similar for both groups, and there was no mortality after stage 1 in either group.

In stage 2, the blood losses (P = 0.051) and surgical times (P = 0.005) were higher in the TSH group than in the T-ALPPS group; there were no differences regarding transfusion and hospital stay. Overall morbidity (9 cases in TSH vs. 10 cases in T-ALPPS), $\geq$ IIIB complications (3 in TSH vs. 2 in T-ALPPS), and PHLF (2 cases in TSH vs. 2 cases in T-ALPPS) were similar in both groups. Mortality after stage 2 was similar in both groups (1 case in TSH and 2 cases in T-ALPPS).

Table 2 Volumetric data. Operative parameters. Morbidity and mortality

Before matching with PSM				After matching with PSM		
Parameter	TSH (n = 41)	T-ALPPS (n = 34)	p	TSH (n = 21)	T-ALPPS (n = 21)	p
Volumetry data						
FLR stage 1. %	31 (20–43)	28 (17–37)	0.051	33 (27–43)	28 (17–37)	0.003
FLR stage 2. %	39 (21–65)	41 (30–57)	0.521	40 (36–61)	41 (31–55)	0.321
Increase. %	35 (21–86)	69 (19–137)	0.001	39 (21–66)	68 (21.8–100)	0.018
Interval. days	37 (21–60)	15.5 (9–33)	0.001	45 (28–60)	15 (9–31)	0.001
Kinetic growth. ml/day	7.2 (1.41–16.9)	18.5 (1.1–60.9)	0.001	10.1 (1.4–16.9)	18.6 (1.1–32.6)	0.001
Intraoperative data						
Stage 1						
Blood loss, ml	150 (50–300)	100 (50–200)	0.877	250 (50–500)	70 (40–800)	0.415
Patients transfused	1	1	0.711	1	1	1
Surgical time, min	120 (90–400)	150 (100–240)	0.008	120 (90–400)	180 (100–240)	0.024
Hospital stay, days	5 (3–12)	5.5 (3–21)	0.18	5 (4–10)	6 (3–21)	0.054
Stage 2						
Blood loss, ml	500 (50–1500)	400 (80–1000)	0.028	600 (50–1500)	400 (90–1500)	0.051
Patients transfused	8	6	0.177	6	4	0.258
Surgical time, min	210 (120–420)	150 (90–300)	0.001	180 (150–300)	170 (90–210)	0.005
Hospital stay, days	8 (4–72)	9 (4–93)	0.456	8.5 (4–50)	10 (4–93)	0.530
Right trisectionectomy	7	11	0.173	4	6	0.154
Complications						
Stage 1						
Global morbidity	4	9	0.02	2	6	0.116
Morbidity ≥ IIIB	1	2	0.449	1	1	1
PHLF	0	1	1	0	1	1
Stage 2						
Global morbidity	11	12	0.564	9	10	0.757
Morbidity ≥ IIIB	5	4	0.858	3	2	0.634
PHLF	7	5	0.673	2	2	1
Mild PHLF	7	3		2	1	
Severe PHLF	0	2		0	1	
Mortality	2	2	1	1	2	0.549

FLR future liver remnant; *PHLF* post-hepatectomy liver failure

Discussion

The oncological outcomes for patients with CRLM operated on by TSH and T-ALPPS were similar, but there is the advantage of higher resectability for T-ALPPS (100% for T-ALPPS vs. 90.5% for TSH). Before PSM there were differences in the median number of nodules, which were higher in the TSH group, while the median size was higher in the T-ALPPS group. These findings were related to the greater indication for ALPPS in patients with large liver metastases occupying the right lobe with a very small left lateral sector. After PSM, the two groups were homogeneous regarding preoperative CEA levels, number and size of nodules, bilobar disease, and neoadjuvant chemotherapy received—including the use of biological agents.

The initial publication from the ALPPS registry [11] showed the best oncological results for patients with CRLM, with a 1-year OS and DFS of 81% and 59%, respectively. These similar results were communicated in some hospital series [12, 26, 27]. However, other studies [13, 28, 29] reported worse long-term outcomes, especially in terms of early recurrence. Oldhafer et al. [13] reported an 85.7% recurrence with a median of 8 months. In our series, although recurrence within the first year after T-ALPPS was also higher than in TSH, DFS was similar at 3 and 5 years.

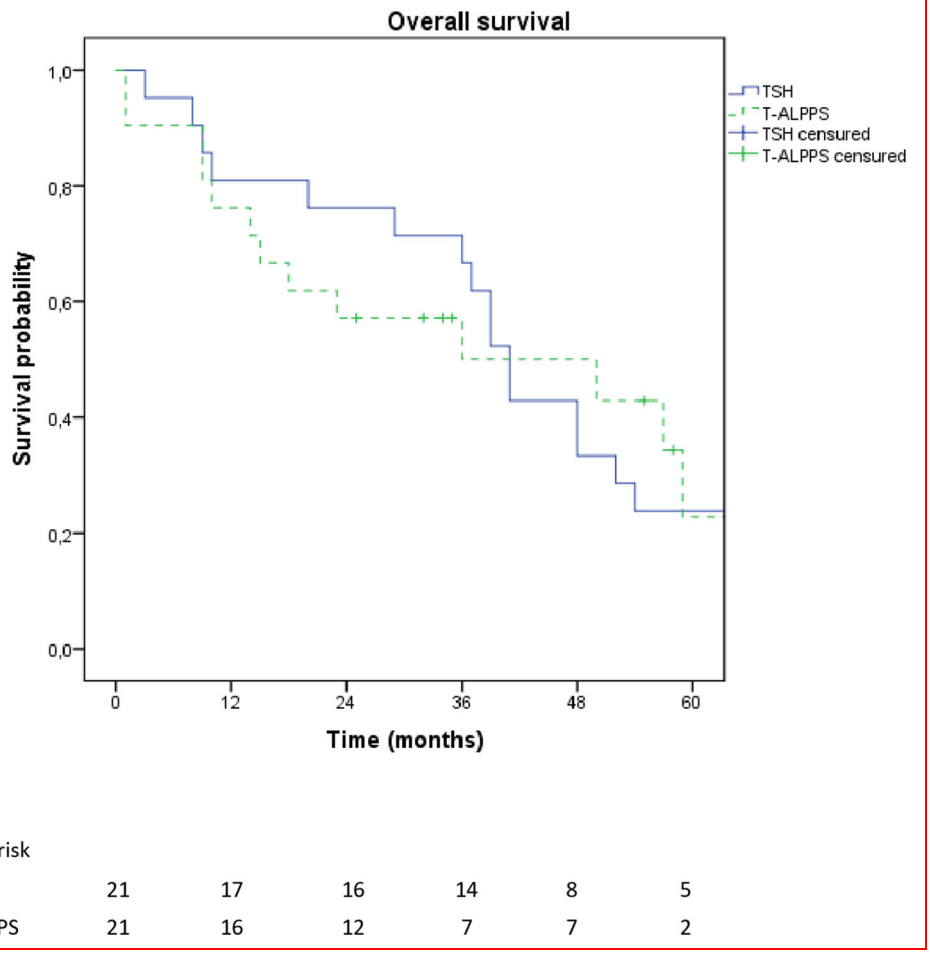

Fig. 1 Overall survival of TSH versus T-ALPPS ($p = 0.925$)

Adam et al. [15] compared 17 patients with ALPPS to 41 patients with TSH, in which there was a dropout rate of 36.6% in TSH vs. 0% in ALPPS. Overall survival at 2 years was significantly lower after ALPPS than after TSH (42% vs. 77%, respectively) ($P = 0.006$), but there was no significant difference in DFS (1-year DFS was 0% vs. 10% for the TSH group). In the present series, the 1-year DFS (70.6% for TSH and 44.6% for T-ALPPS) was higher than the one reported by Adam et al. Another retrospective study [30] has reported similar results to ours (one-year DFS for TSH was 80% vs. 67% for ALPPS), and a recent publication from the LIGRO trial communicates similar recurrence within 12 months after TSH and ALPPS [18].A drawback of TSH is the dropout rate of 5–30% that was related to prolonged regeneration or insufficient hypertrophy [7, 9, 31]. The prolonged regeneration could cause tumor progression; therefore, to avoid dropout most authors suggest administering inter-stage chemotherapy [6]. For some authors [32–34], this long period of regeneration allows the selection of patients avoiding surgical operations during tumor progression. In our experience, the dropout rate was also higher in the TSH group (resectability of 90.6% vs. 100% for T-ALPPS). The resectability for TSH in the Scandinavian randomized controlled trial (LIGRO trial [17]) was only 57%, mainly due to an attenuated hypertrophy (with higher rate of crossover from TSH to ALPPS than in others series), and it was probably related to the short time established as treatment failure (8 weeks to achieve an FLR higher than 30%) contrary to the longer time interval (between 4 and 12 weeks) used by most authors [15, 31]. Due to the greater resectability and the greater volume increase obtained with ALPPS, we suggest that it could be indicated in case of a very low FLR with the consequent need for a large increase in volume in a very short period of time in order to avoid tumor progression. This accounts for the possibility of a 30% dropout rate for TSH, even with inter-stage chemotherapy (as suggested by Adam et al.). The presence of extrahepatic disease or advanced liver disease should be controlled initially with neoadjuvant chemotherapy since the patient will undergo two consecutive interventions in a short time and the period without chemotherapy could be prolonged, especially if postoperative complications manifest. For these reasons, we

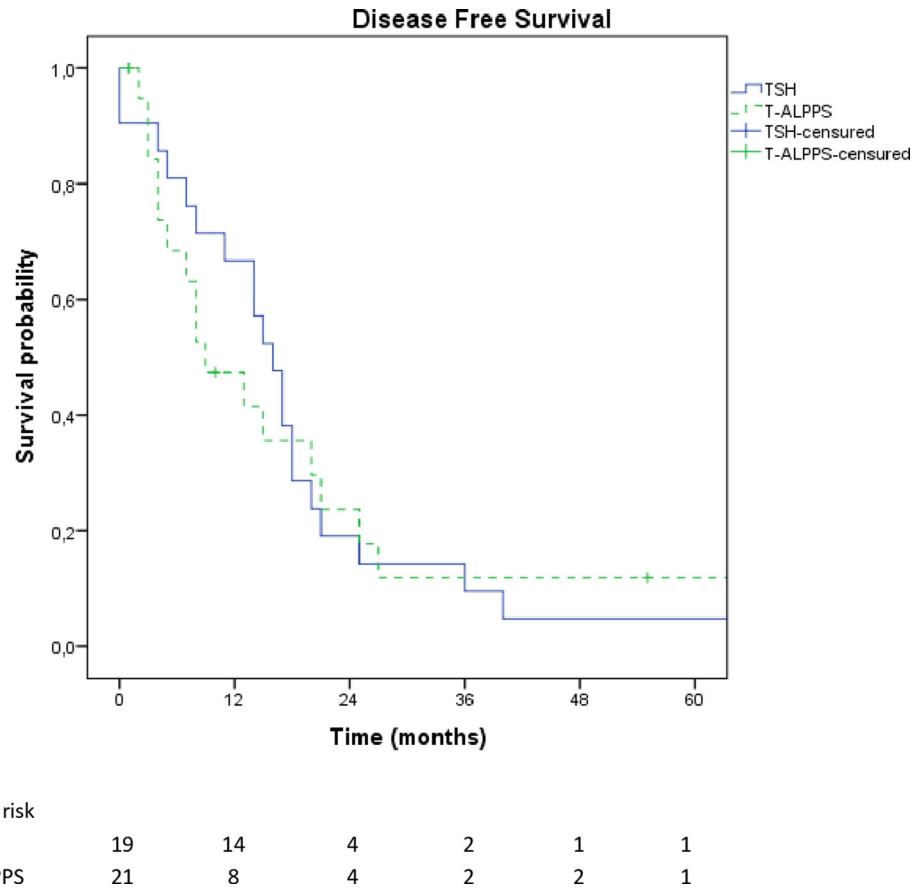

Fig. 2 Disease-free survival of TSH versus T-ALPPS ($p = 0.930$)

consider either the presence of a high hepatic tumor load or extrahepatic disease not controlled by neoadjuvant chemotherapy to be an absolute contraindication for ALPPS. The initial mortality of ALPPS was very high [10, 19, 20, 35]; better results were reported in young patients with CRLM [11]. In some recent publications from the ALPPS World Registry [36–38], the mortality related to ALPPS is decreasing, especially in centers with greater experience. The use of risk adjustment in patient selection and the use of less invasive techniques in stage 1 were independent factors related to a decrease in mortality (from the initial 17% to 4% in 2015) [37]. Mortality in our series was similar in both groups, and it was comparable to the results obtained in the first randomized trial (8.3% mortality rate for ALPPS vs. 9.1% for TSH) [17]. In other comparative series, the results are contradictory. For some authors [30, 39–41], the mortality rate was higher with ALPPS than with TSH; for Adam et al. [15], the mortality rate was higher in TSH (0% in ALPPS vs. 5% in TSH).

This study has two fundamental limitations: Firstly, it is a retrospective study that covers a long period of time. However, as far as we know, it is one of the largest series published by a single center. Secondly, the two techniques were used in two different periods of time. To resolve these complications, we performed a PSM to homogenize the groups. After the PSM, we concluded that T-ALPPS could be a safe and effective alternative, with results comparable to TSH but the advantage of being able to offer a curative hepatectomy to all patients. Therefore, we consider T-ALPPS to be indicated in patients with CRLM with an insufficient FLR in those who need to achieve rapid regeneration.

References

1. Adam R, De Gramont A, Figueras J et al (2012) The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. Oncologist 17:1225–1239
2. Van Cutsem E, Cervantes A, Adam R et al (2016) ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 27:1386–1422
3. Adam R, Delvart V, Pascal G, et al (2004) Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 240:644–657; discussion 657–648
4. Wicherts DA, de Haas RJ, Adam R (2007) Bringing unresectable liver disease to resection with curative intent. Eur J Surg Oncol 33(Suppl 2):S42–51

5. Makuuchi M, Thai BL, Takayasu K et al (1990) Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery 107:521–527
6. Adam R, Laurent A, Azoulay D et al (2000) Two-stage hepatectomy: a planned strategy to treat irresectable liver tumors. Ann Surg 232:777–785
7. Pamecha V, Levene A, Grillo F et al (2009) Effect of portal vein embolisation on the growth rate of colorectal liver metastases. Br J Cancer 100:617–622
8. Pandanaboyana S, Bell R, Hidalgo E et al (2015) A systematic review and meta-analysis of portal vein ligation versus portal vein embolization for elective liver resection. Surgery 157:690–698
9. Passot G, Chun YS, Kopetz SE et al (2016) Predictors of safety and efficacy of 2-stage hepatectomy for bilateral colorectal liver metastases. J Am Coll Surg 223:99–108
10. Schnitzbauer AA, Lang SA, Goessmann H et al (2012) Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 255:405–414
11. Schadde E, Ardiles V, Robles-Campos R, et al (2014) Early survival and safety of ALPPS: first report of the International ALPPS Registry. Ann Surg 260:829–836; discussion 836–828
12. Hernandez-Alejandro R, Bertens KA, Pineda-Solis K et al (2015) Can we improve the morbidity and mortality associated with the associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) procedure in the management of colorectal liver metastases? Surgery 157:194–201
13. Oldhafer KJ, Donati M, Jenner RM et al (2014) ALPPS for patients with colorectal liver metastases: effective liver hypertrophy, but early tumor recurrence. World J Surg 38:1504–1509
14. Olthof PB, Huiskens J, Wicherts DA et al (2017) Survival after associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) for advanced colorectal liver metastases: A case-matched comparison with palliative systemic therapy. Surgery 161:909–919
15. Adam R, Imai K, Castro Benitez C et al (2016) Outcome after associating liver partition and portal vein ligation for staged hepatectomy and conventional two-stage hepatectomy for colorectal liver metastases. Br J Surg 103:1521–1529
16. Baumgart J, Jungmann F, Bartsch F, et al (2019) Two-stage hepatectomy and ALPPS for advanced bilateral liver metastases: a tailored approach balancing risk and outcome. J Gastrointest Surg. https://doi.org/10.1007/s11605-019-04145-9
17. Sandstrom P, Rosok BI, Sparrelid E, et al (2018) ALPPS improves resectability compared with conventional two-stage hepatectomy in patients with advanced colorectal liver metastasis: results from a Scandinavian multicenter randomized controlled trial (LIGRO trial). Ann Surg 267:833–840
18. Rosok BI, Host-Brunsell T, Brudvik KW, et al (2019) Characterization of early recurrences following liver resection by ALPPS and two stage hepatectomy in patients with colorectal liver-metastases and small future liver remnants; a translational substudy of the LIGRO-RCT. HPB (Oxford). https://doi.org/10.1016/j.hpb.2018.12.003
19. Nadalin S, Capobianco I, Li J et al (2014) Indications and limits for associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). Lessons Learned from 15 cases at a single centre. Z Gastroenterol 52:35–42
20. Torres OJ, Fernandes Ede S, Oliveira CV et al (2013) Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): the Brazilian experience. Arq Bras Cir Dig 26:40–43
21. Robles R, Parrilla P, Lopez-Conesa A, et al (2014) Tourniquet modification of the associating liver partition and portal ligation for staged hepatectomy procedure. Br J Surg 101:1129–1134; discussion 1134
22. Robles R, Marin C, Lopez-Conesa A et al (2012) Comparative study of right portal vein ligation versus embolisation for induction of hypertrophy in two-stage hepatectomy for multiple bilateral colorectal liver metastases. Eur J Surg Oncol 38:586–593
23. Dindo D, Demartines N, Clavien P-A (2004) Classification of surgical complications. Ann Surg 240:205–213
24. Rahbari NN, Garden OJ, Padbury R et al (2011) Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 149:713–724
25. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
26. Lang SA, Loss M, Benseler V et al (2015) Long-term results after in-situ split (ISS) liver resection. Langenbecks Arch Surg 400:361–369
27. Alvarez FA, Ardiles V, de Santibanes M et al (2015) Associating liver partition and portal vein ligation for staged hepatectomy offers high oncological feasibility with adequate patient safety: a prospective study at a single center. Ann Surg 261:723–732
28. Bjornsson B, Sparrelid E, Rosok B et al (2016) Associating liver partition and portal vein ligation for staged hepatectomy in patients with colorectal liver metastases—intermediate oncological results. Eur J Surg Oncol 42:531–537
29. Kremer M, Manzini G, Hristov B et al (2015) Impact of neoadjuvant chemotherapy on hypertrophy of the future liver remnant after associating liver partition and portal vein ligation for staged hepatectomy. J Am Coll Surg 221:717–728.e711
30. Ratti F, Schadde E, Masetti M et al (2015) Strategies to increase the resectability of patients with colorectal liver metastases: a multi-center case-match analysis of ALPPS and conventional two-stage hepatectomy. Ann Surg Oncol 22:1933–1942
31. Wicherts DA, Miller R, de Haas RJ et al (2008) Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. Ann Surg 248:994–1005
32. Adam R, Pascal G, Castaing D et al (2004) Tumor progression while on chemotherapy. Ann Surg 240:1052–1064
33. Narita M, Oussoultzoglou E, Jaeck D et al (2011) Two-stage hepatectomy for multiple bilobar colorectal liver metastases. Br J Surg 98:1463–1475
34. Simoneau E, Hassanain M, Shaheen M et al (2015) Portal vein embolization and its effect on tumour progression for colorectal cancer liver metastases. Br J Surg 102:1240–1249
35. Serenari M, Zanello M, Schadde E et al (2016) Importance of primary indication and liver function between stages: results of a multicenter Italian audit of ALPPS 2012–2014. HPB (Oxford) 18:419–427
36. Linecker M, Stavrou GA, Oldhafer KJ et al (2016) The ALPPS risk score: avoiding futile use of ALPPS. Ann Surg 264:763–771
37. Linecker M, Bjornsson B, Stavrou GA et al (2017) Risk adjustment in ALPPS is associated with a dramatic decrease in early mortality and morbidity. Ann Surg 266:779–786
38. Schadde E, Raptis DA, Schnitzbauer AA, et al (2015) Prediction of mortality after ALPPS stage-1: an analysis of 320 patients from the international ALPPS registry. Ann Surg 262:780–785; discussion 785–786
39. Schadde E, Ardiles V, Slankamenac K et al (2014) ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumors compared with conventional-staged hepatectomies: results of a multicenter analysis. World J Surg 38:1510–1519

40. Shindoh J, Vauthey JN, Zimmitti G, et al (2013) Analysis of the efficacy of portal vein embolization for patients with extensive liver malignancy and very low future liver remnant volume, including a comparison with the associating liver partition with portal vein ligation for staged hepatectomy approach. J Am Coll Surg 217:126–133; discussion 133–124
41. Moris D, Ronnekleiv-Kelly S, Kostakis ID et al (2018) Operative results and oncologic outcomes of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) versus two-stage hepatectomy (TSH) in patients with unresectable colorectal liver metastases: a systematic review and meta-analysis. World J Surg 42:806–815