European Journal of Surgical Oncology 49 (2023) 550–559

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Review Article

Two stage hepatectomy (TSH) versus ALPPS for initially unresectable colorectal liver metastases: A systematic review and meta-analysis

Tamara Díaz Vico [a, b, *], Pablo Granero Castro [a, c], Laura Alcover Navarro [d], Aida Suárez Sánchez [e], Luka Mihic Góngora [f], Eva María Montalvá Orón [g, h], Javier Maupoey Ibáñez [g], Nuria Truán Alonso [i], Ignacio González-Pinto Arrillaga [a, c], José Electo Granero Trancón [c, i]

[a] Department of HPB Surgery and Transplantation Unit, Division of General Surgery, Hospital La Fe and Hepatology, HBP Surgery and Transplants, IIS La Fe, Valencia, Spain
[b] Health Research Institute of the Principality of Asturias (ISPA), Spain
[c] Department of Surgery, University of Oviedo, Spain
[d] Department of Anaesthesiology, Hospital Universitario Central de Asturias (HUCA), Oviedo, Spain
[e] Department of General Surgery, Hospital Universitario San Agustín (HUSA), Avilés, Spain
[f] Department of Medical Oncology, Hospital Universitario Central de Asturias (HUCA), Oviedo, Spain
[g] Department of HPB Surgery and Transplantation Unit, Division of General Surgery, Hospital La Fe, Valencia, Spain
[h] CIBERehd, Instituto de Salud Carlos III, Madrid, Spain and Hepatology, HBP Surgery and Transplants, IIS La Fe, Valencia, Spain
[i] Department of Colorectal Surgery, Division of General Surgery, Hospital Universitario Central de Asturias (HUCA), Oviedo, Spain

ARTICLE INFO

Article history:
Received 28 April 2022
Received in revised form
3 October 2022
Accepted 3 November 2022
Available online 9 November 2022

Keywords:
Unresectable colorectal liver metastases
TSH
ALPPS
Portal vein ligation
Portal vein embolization
Future liver remnant

ABSTRACT

Background: Although numerous comparisons between conventional Two Stage Hepatectomy (TSH) and Associating Liver Partition and Portal Vein Ligation for staged hepatectomy (ALPPS) have been reported, the heterogeneity of malignancies previously compared represents an important source of selection bias. This systematic review and meta-analysis aimed to compare perioperative and oncological outcomes between TSH and ALPPS to treat patients with initially unresectable colorectal liver metastases (CRLM).
Methods: Main electronic databases were searched using medical subject headings for CRLM surgically treated with TSH or ALPPS. Patients treated for primary or secondary liver malignancies other than CRLM were excluded.
Results: A total of 335 patients from 5 studies were included. Postoperative major complications were higher in the ALPPS group (relative risk [RR] 1.46, 95% confidence interval [CI] 1.04–2.06, $I^2 = 0\%$), while no differences were observed in terms of perioperative mortality (RR 1.53, 95% CI 0.64–3.62, $I^2 = 0\%$). ALPPS was associated with higher completion of hepatectomy rates (RR 1.32, 95% CI 1.09–1.61, $I^2 = 85\%$), as well as R0 resection rates (RR 1.61, 95% CI 1.13–2.30, $I^2 = 40\%$). Nevertheless, no significant differences were achieved between groups in terms of overall survival (OS) (RR 0.93, 95% CI 0.68–1.27, $I^2 = 52\%$) and disease-free survival (DFS) (RR 1.08, 95% CI 0.47–2.49, $I^2 = 54\%$), respectively.
Conclusion: ALPPS and TSH to treat CRLM seem to have comparable operative risks in terms of mortality rates. No definitive conclusions regarding OS and DFS can be drawn from the results.
© 2022 Elsevier Ltd, BASO ~ The Association for Cancer Surgery, and the European Society of Surgical Oncology. All rights reserved.

1. Introduction

Despite recent advances in chemotherapy regimens, surgery remains the cornerstone of curative treatment of colorectal liver metastases (CRLM), achieving 5-year survival rates of up to 50% [1]. The definition of resectability has evolved over the years. In 2006, The Americas Hepato-Pancreato-Biliary Association (AHPBA) Consensus Conference stated that the indication of resection depended on the presence of sufficient future liver remnant (FLR) after complete (R0) resection. Unfortunately, only 25% of patients

* Corresponding author. Division of General Surgery, Hospital Universitario Central de Asturias (HUCA), Avenida de Roma s/n, 33011, Oviedo, Asturias, Spain.
E-mail address: tamara.diaz.vico@gmail.com (T. Díaz Vico).

https://doi.org/10.1016/j.ejso.2022.11.010
0748-7983/© 2022 Elsevier Ltd, BASO ~ The Association for Cancer Surgery, and the European Society of Surgical Oncology. All rights reserved.

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 20, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

Table 1
Risk of bias assessment (Newcastle-Ottawa quality assessment scale criteria and Jadad scale).

Newcastle-Ottawa scale	Selection				Comparability		Outcome		Quality score
Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort from same source as exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-Up Long Enough for Outcome to Occur	Adequacy of Follow-Up	
Ratti et al. (2015)	Patients who underwent ALPPS for CRLM at three tertiary hospitals in Italy were compared with a cohort of patients who underwent TSH for CRLM at a single institution.*	Yes*	Surgical records*	Yes*	The ALPPS group was matched based on a 1:3 ratio with patients who underwent TSH, including seven covariates: age, associated comorbidities, number of chemotherapy cycles, primary tumor location, number of liver lesions, synchronous presentation, and extent of hepatectomy.	Medical records*	Yes*	1-year overall survival was 92 and 94% for ALPPS and TSH group respectively.*	Good
Adam et al. (2016)	Patients who underwent TSH or ALPPS for colorectal liver metastases at one institution.*	Yes*	Surgical records*	Yes*	No adjustement of confounders was performed.*	Medical records*	Yes*	Only five patients in the TSH group remained alive after 3 years of follow-up. *	Good
Kambakamba et al. (2016)	Patients who underwent TSH or ALPPS for CRLM at two tertiary institutions.*	Yes*	Surgical records*	Yes*	Data on comparable variables were obtained from medical records. No adjustement of confounders was performed.*	Medical records*	Yes*	5-year overall survival was described without losses in follow-up. *	Good
Baumgart et al. (2019)	Patients who underwent TSH or ALPPS for colorectal liver metastases at one institution.*	Yes*	Surgical records*	Yes*	Data on comparable variables were obtained from medical records. No adjustement of confounders was performed.*	Medical records*	Yes*	Median overall survival after TSH and ALPPS was 26.7 months and 36.2 months respectively.*	Good

Jadad scale	Randomisation	Double-blinding	Withdrawals and dropouts	Total
Sandström et al. (2018)	2 points	Not blinded. 0 points	1 point	3 points

Good quality: 3 or 4 stars (*) in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain; *Fair quality:* 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; *Poor quality*: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.
ALPPS: associating liver partition and portal vein ligation for staged hepatectomy; TSH: two-staged hepatectomy; CRLM: colorectal liver metastases.

with CRLM are deemed suitable for resection [2], either at diagnosis or after conversion therapy.

Lately, in patients with initially unresectable CRLM, the addition of cetuximab to the classical chemotherapy doublet regimen or the use of a triplet regimen with the addition of bevacizumab or cetuximab was reported to achieve resection rates of up to 61% [3–5] and 55% [6–8], respectively. The relationship between objective response rate and resection rate in clinical trials involving patients with initially unresectable CRLM increases when resection is included as a secondary study end-point [9]. Therefore, evaluation by a multidisciplinary team is a key factor in selecting patients suitable for resection [10].

Two-stage hepatectomy (TSH) including portal vein ligation or portal vein embolization in the first stage to induce hypertrophy of the FLR has been developed in an attempt to allow resection in patients with insufficient FLR [11–13]. In 2000, Adam et al. described the TSH technique for patients with bilateral multinodular CRLM [14]. The greatest drawback of this approach, described in nearly one third of patients in whom TSH is planned [15], is the risk of tumor progression during the 4–8 weeks required for the FLR hypertrophy needed to avoid post-hepatectomy liver failure (PHLF) [16]. Survival rates reported in patients not proceeding to second stage resection are lower than in patients treated with chemotherapy alone [14,15,17,18].

In 2011, a new TSH technique was described [19]. This technique, designated as Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS), consists of a combination of portal vein ligation and in situ parenchymal transection during the first-stage hepatectomy, allowing faster regeneration of the FLR and reducing the possibility of tumor progression. However, morbidity and mortality rates of up to 60% and 15%, respectively, were initially reported, representing major disadvantages of this technique [20]. Nevertheless, after the creation of the international ALPPS registry (www.ALPPS.org) with increased levels of experience, major Clavien-Dindo complications, and 90-day mortality rates, were comparable to those in patients undergoing TSH, but with a completion rate of 98% [21]. Recently, benchmark values for ALPPS have been described demonstrating that the ALPPS procedure performed in low-risk patients (*ie* younger age, high-volume center and favorable tumor type) is associated with low morbidity and mortality and matches those of major hepatic surgery or any other abdominal surgery [22–24].

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 20, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

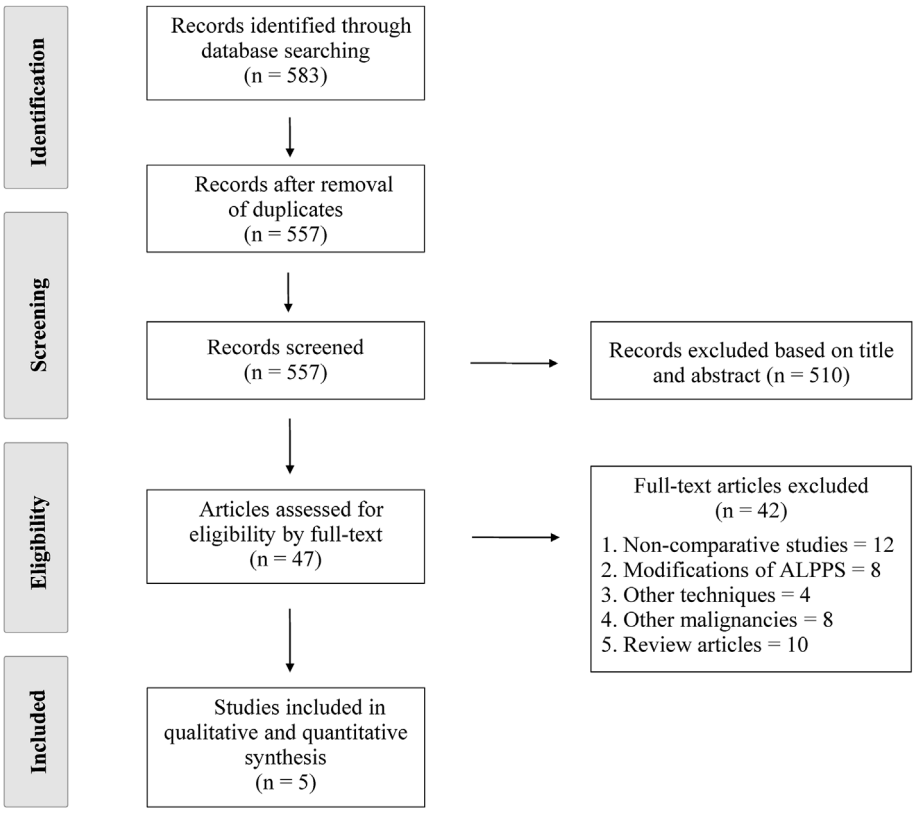


Fig. 1. PRISMA study flow diagram.

Although numerous comparisons between TSH and ALPPS have been reported in terms of complications, completion rates and liver regeneration efficiency, the heterogeneity of patients and, mainly, the wide variety of different malignancies compared in previous studies, such as hepatocellular carcinomas, neuroendocrine tumors, hilar and intrahepatic cholangiocarcinoma, gallbladder tumors, etc., represent an important source of selection bias [25–28]. While attempts have been made to compare both techniques with the published data, no large comparative study regarding CRLM is currently available. Accordingly, this systematic review and meta-analysis aimed to assess the safety and feasibility of TSH compared to ALPPS only for initially unresectable CRLM, perioperative outcomes and its effect on locoregional recurrences, as well as to evaluate overall survival (OS) and disease-free survival (DFS).

2. Methods

Only articles published since 2011 when ALPPS was first reported, involving humans and written in English that compared TSH versus ALPPS with initially unresectable colorectal liver metastases (FLR <30%), were included. Exclusion criteria included patients treated for primary or secondary liver malignancies other than CRLM.

Primary end-points included [1] volumetric outcomes: percentage of FLR increase and time between stage one and two; and [2] perioperative outcomes: surgery duration, blood loss and red blood cell transfusion, postoperative adverse events, perioperative mortality, completion of both stages, and margin-negative (R0) resection rate. Secondary end-points included oncological outcomes: OS and DFS.

In order to be included in this meta-analysis, studies [1] had to report on at least one of the primary end-points and [2] had to indicate how many patients underwent the procedure. Studies were excluded from the review if [1] primary end-points were not clearly reported, and [2] the surgical technique was unclear to ascertain ALPPS.

2.1. Search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase (via Ovid), and CINAHL (via EBSCO) from 2011 to present were searched using a combination of medical subject heading (MeSH) and key terms on TSH and ALPPS. Search terms included “two stage hepatectomy” OR “TSH”, “associating liver partition and portal vein ligation for staged hepatectomy” OR “ALPPS”, “portal vein ligation” OR “PVL” and “portal vein embolization” OR “PVE”, and any derivatives of these terms. Searching for the studies was done by hand by screening abstracts and full texts when necessary. An additional manual search included references listed in already identified studies, relevant review articles, and journals’ tables of content. One of the authors developed the search strategies. The first search was run in September 2019 and updated in December 2021.

2.2. Data collection and analysis

Two different authors (PG and TDV) reviewed the articles eligible for the review and extracted variables concerning first author, year of publication, study population demographics, study design, inclusion and exclusion criteria of each study, tumor-related characteristics, chemotherapy-related regimens, regeneration efficiency of FLR, operative variables related to the surgical procedures, and oncological outcomes. Discrepancies between reviewers were resolved after discussion between them and two senior authors

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 20, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

Table 2a
Demographic variables, tumor characteristics and neoadjuvant treatment of ALPPS *versus* TSH for CRLM.

			Ratti et al. (2015)		Adam et al. (2016)		Kambakamba et al. (2016)		Sandström et al. (2018)		Baumgart et al. (2019)	
Study design			Retrospective multicentric case-control study		Retrospective cohort study		Retrospective multicentric cohort study		Multicentric RCT		Retrospective cohort study	
Patients			**ALPPS (n = 12)**	**TSH (n = 36)**	**ALPPS (n = 17)**	**TSH (n = 41)**	**ALPPS (n = 43)**	**TSH (n = 31)**	**ALPPS (n = 48)**	**TSH (n = 49)**	**ALPPS (n = 8)**	**TSH (n = 50)**
Demographics	Age		59 (51–79)	59 (42–66)	58 (23–75)	58 (32–75)	58 (49–66)		65.4 ± 8.9	64.9 ± 11.7	52 (37–69)	58 (35–78)
	Male sex		5 (41.7%)	19 (52.8%)	12 (70%)	23 (56%)	40 (54.1%)		32 (67%)	36 (73%)	4 (50%)	36 (72%)
	ASA I/II/III/IV		0/9/3/0	2/24/9/1	2/11/14/0	4/33/4/0	N/A		12/32/4	12/28/9	N/A	
	BMI		25 (21–29)	22.5(19 –28)	N/A		N/A		24.9 ± 3.3*	26.4 ± 3.5*	N/A	
Tumor characteristics	Primary tumor location	Colon	9 (75%)	25 (69.4%)	13 (76%)	27 (66%)	N/A		28 (58%)	29 (59%)	4 (50%)	34 (68%)
		Rectum	3 (25%)	11 (30.6%)	4 (23%)	14 (34%)	N/A		20 (42%)	20 (41%)	4 (50%)	16 (32%)
	T-stage primary tumor 1–2/3-4		0/12	2/34	1/15	4/30	7/67		N/A		4/4	6/42
	N-stage primary tumor 0/1-2		7/5	12/24	3/13	6/27	13/61		N/A		3/5	12/36
	Synchronous/metachronous		5/7	13/23	15/2	38/3	63/11		N/A		6/2	42/8
	Number of lesions (1–5/6-10/11-)		4 (1–11)	5 (1–13)	10 (3–20)	10 (2–35)	5 (3.0–8.6)		(16/21/11)	(15/15/19)	N/A	
	Largest tumor size (mm)		44 ± 17.6	38 ± 25	40 (13–145)	50 (10 –150)	N/A		54 ± 41	49 ± 39	N/A	
	Extrahepatic disease		N/A		6 (35%)	12 (29%)	3 (4%)		0	9 (18%)	7 (14%)	7 (14%)
Neoadjuvant treatment	Neoadjuvant chemotherapy		9 (75%)	30 (83%)	17 (100%)	41 (100%)	39 (90%)	28 (90%)	47 (98%)	48 (98%)	7(87%)	46(92%)
	Preoperative chemotherapy cycles		6 (2–12)	6 (4–9)	8 (4–37)	11 (4–32)	6 (5–8)	6 (4–7)	6 ± 4	7 ± 4	N/A	
	Chemotherapy regimen	Oxaliplatin based	5 (41.7%)	12 (33.3%)	13 (76%)	27 (66%)	21 (49%)	14 (45%)	26 (54%)	29 (59%)	N/A	
		Irinotecan based	5 (41.7%)	18 (50%)	6 (35%)	17 (41%)	12 (16%)	12 (39%)	20 (41%)	16 (32%)	N/A	
		Capecitabine based	–	–	N/A	N/A	6 (14%)	4 (13%)	4 (8%)	5 (10%)	N/A	
		Biologic agents	5 (41.7%)	15 (41.7%)	15 (88%)	39 (95%)	28 (65%)	18 (58%)	16 (33%)	16 (32%)	45 (78%)	
	Response to chemotherapy (RECIST)	Stable disease	N/A		N/A	N/A	4 (11%)	4 (14%)	9 (18%)	10 (20%)	N/A	
		Partial response	N/A		N/A	N/A	30 (77%)	25 (89%)	38 (79%)	38 (77%)	N/A	
		Progression	N/A		2 (11%)	4 (9%)	2 (5%)	2 (7%)	–	–	N/A	

RCT: randomized controlled trial; ALPPS: associating liver partition and portal vein ligation for staged hepatectomy; TSH: two-staged hepatectomy; CRLM: colorectal liver metastases; ASA: American Society of Anesthesiologists; BMI: body mass index; FLR: future liver remnant. N/A: not assessed; *: statistically significant. Data are expressed as number of cases and percentages or range in parenthesis.

Descargado para Lucia Angulo (lu.manu26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 20, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

Table 2b
Volumetric, perioperative and oncological outcomes of ALPPS *versus* TSH for CRLM.

		Ratti et al. (2015)		Adam et al. (2016)		Kambakamba et al. (2016)		Sandström et al. (2018)		Baumgart et al. (2019)	
Patients		**ALPPS (n = 12)**	**TSH (n = 36)**	**ALPPS (n = 17)**	**TSH (n = 41)**	**ALPPS (n = 43)**	**TSH (n = 31)**	**ALPPS (n = 48)**	**TSH (n = 49)**	**ALPPS (n = 8)**	**TSH (n = 50)**
Operative details	Red blood cell transfusion stage 1	6*	2*	4*	2*	N/A		N/A		N/A	
	Blood loss stage 1 (ml)	N/A		600(300 −2000)*	200(100 −1700)*	N/A		762 ± 660*	141 ± 182*	N/A	
	Red blood cell transfusion stage 2	4*	4*	4*	8*	N/A		N/A		N/A	
	Blood loss stage 2 (ml)	N/A		500(50 −3100)	700(170 −4000)	N/A		234 ± 454*	1009 ± 658*	N/A	
	Operative time stage 1 (min)	276 (138 −450)*	150 (120 −310)*	404 (260 −668)	337 (190 −700)	N/A		N/A		N/A	
	Operative time stage 2 (min)	185 (50 −210)*	300 (190 −370)*	243 (138 −540)*	385 (190 −610)*	N/A		N/A		N/A	
	Minor Complications (Clavien1-2)	7 (58.3%)*	8 (22.2%)*	10 (59%)*	6 (15%)*	N/A		N/A		N/A	
	Major Complications (Clavien 3–4)	5 (41.7%)*	6 (17.6%)*	7 (41%)	16 (39%)	9 (21%)	5 (16%)	19(43%)	12 (43%)	4(50%)	17(34%)
	Completion of both stages	12 (100%)	34 (94%)	17 (100%)*	26 (63%)*	64 (86%)		44(92%)*	28 (57%)*	8(100%)*	39(78%)*
	Mortality Length of stay (days)	1 (8.3%)* 24 [16–42]	1 (2.9%)* [18] [14–38]	0 N/A	2 (5%)	5 (11%) N/A	2 (6%)	4 (8%) [23] [17]	3 (6%) [18] [14]	1(12%) 23.5 (20–66)	2(4%) 9.5 (7-65)1 8.5 (7-25)2
	Resection margin (R0)	N/A		2 (11%)	5 (19%)	54 (73%)		34(77%)	16 (57%)	8(100%)	35(89%)
Volumetric outcomes	% FLR increase	47 (38 −133)	41 (29–79)	24 (11–38)	30 (19–53)	N/A		68 ± 38*	36 ± 18*	N/A	
	% FLR before second stage	36	34.5	36 (26–49)	40 (25–55)	N/A		37.1*	26.1*	N/A	
	Time between stage 1 and 2 (days)	11 (7–12)*	31 (25 −39)*	12 (9–39)*	103(19 −450)*	N/A		11 ± 11*	43 ± 15*	7(6–11)	58–70
Oncologic outcomes	Local recurrence	N/A		8 (47%)	9 (21.9%)	28 (37.8%)		N/A		87.5%	60%
	Overall survival (months)	92 (12)	94 (12)	72 (24)	95 (24)	41 (24.7)	23 (29.3)	N/A		36.2(11.3 −61.2)	26.7(21.8 −35.1)
	Disease-free survival (months)	67 (12)	80 (12)	0 (12)	10 (12)	36 (10.8)	18 (11)	N/A		3(1.6 −14.8)	5.9(1.7 −18.6)

RCT: randomized controlled trial; ALPPS: associating liver partition and portal vein ligation for staged hepatectomy; TSH: two-staged hepatectomy; ASA: American Society of Anesthesiologists; BMI: body mass index; FLR: future liver remnant. N/A: not assessed; [1]Stage 1; [2]Stage 2; *: statistically significant. Data are expressed as number of cases and percentages or range in parenthesis.

(IGP and JGT). A data extraction form adapted for this review was developed from the 2010 Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) guidelines [29].

2.3. Assessment of risk of bias

Two authors assessed risk of bias independently (LAN and ASS). Quality was assessed using the Jadad scoring system [30] for randomized control trials and the Newcastle-Ottawa scale (NOS) [31] for nonrandomized studies (Table 1).

2.4. Statistical analysis

Statistical analyses were performed in R software (version 4.0.2) [32] with package meta [33]. Analyses comprised only study-level data comparisons rather than individual-level data. For dichotomous outcomes, we used the Mantel-Haenszel method for obtaining the relative risk (RR) and its 95% confidence interval (CI) and restricted maximum-likelihood estimator (REML) to estimate the between-study variance. Survival outcomes were analyzed as dichotomous outcomes with percentage of survival for each endpoint, as we could not obtain hazard ratios (HR) for all studies. We used the method of inverse variance pooling for continuous variables, reporting standardized mean difference (SMD) estimated with Hedges' g method. A random-effects model was used for the meta-analysis of results. Heterogeneity was assessed for the individual meta-analyses by using the I^2 measurement and between-study variance with τ^2. Significant heterogeneity was defined as $p < 0.05$ using the Cochran Q test. Further quantification of heterogeneity was categorized based upon I^2 with values of 25%, 50%, and 75%, indicating low, moderate, and substantial amounts of heterogeneity, respectively.

2.5. Protocol registration

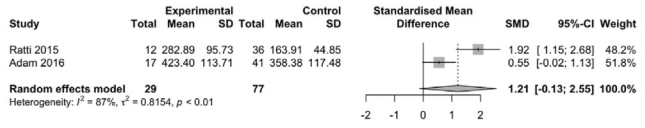
This systematic review was registered in the international PROSPERO database in April 2019 (CRD42019125943), prior to the analysis being undertaken (http://www.crd.york.ad.uk/PROSPERO/) [34].

3. Results

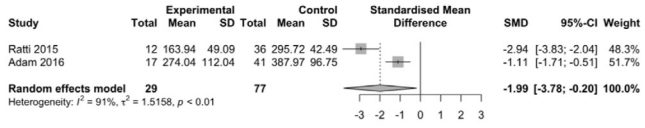
3.1. Study identification and characteristics

Out of a total of five hundred eighty-three citations, 557 studies underwent full-text review, of which 510 were excluded because either they did not fulfill the scientific article structure criterion, the surgical approach described was different or technical variations of the same procedure were conducted, or the studies included malignancies other than CRLM. Overall, 5 studies with a total of 335 involved patients met the inclusion criteria (Fig. 1). The characteristics of the included studies are shown in Table 2a. Of the 5

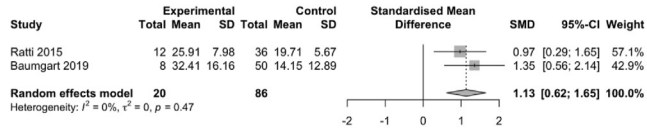
Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 20, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.



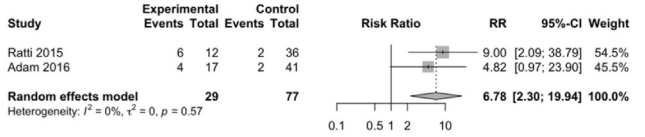
A Meta-analysis of studies on surgery duration (stage 1) of patients undergoing ALPPS vs TSH.



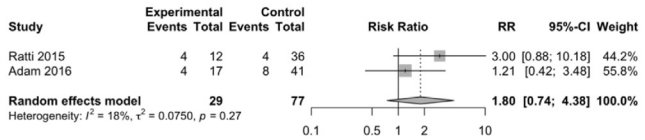
B Meta-analysis of studies on surgery duration (stage 2) of patients undergoing ALPPS vs TSH.



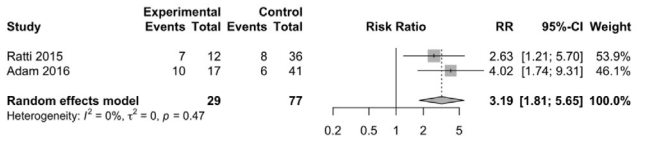
C Meta-analysis of studies on length of stay of patients undergoing ALPPS vs TSH.



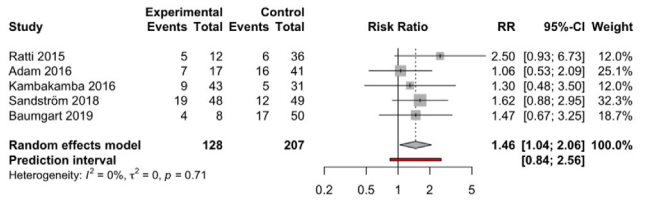
D Meta-analysis of studies on intraoperative red blood cell transfusion (stage 1) of patients undergoing ALPPS vs TSH.



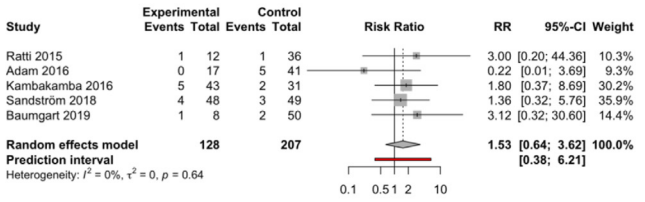
E Meta-analysis of studies on intraoperative red blood cell transfusion (stage 1) of patients undergoing ALPPS vs TSH.



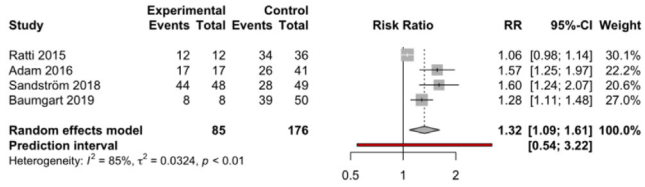
F Meta-analysis of studies on minor complications of patients undergoing ALPPS vs TSH.



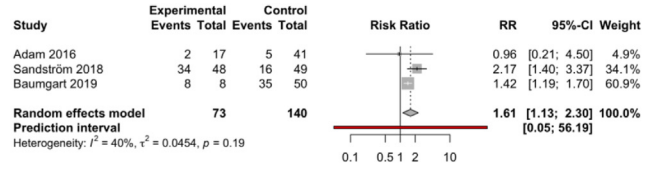
G Meta-analysis of studies on major complications of patients undergoing ALPPS vs TSH.



H Meta-analysis of studies on perioperative mortality of patients undergoing ALPPS vs TSH.



I Meta-analysis of studies on completion of hepatectomy of patients undergoing ALPPS vs TSH.



J Meta-analysis of studies on R0 resection of patients undergoing ALPPS vs TSH.

Fig. 2. Forest plot comparing perioperative outcomes of ALPPS versus TSH. A fixed-effects model was used for the meta-analysis of results. SMD and RR are shown with 95% Cis. **A** Operative time stage 1; **B** Operative time stage 2; **C** Length of stay; **D** Intraoperative red blood cell transfusion stage 1; **E** Intraoperative red blood cell transfusion stage 2; **F** Minor complications; **G** Major complications; **H** Perioperative mortality. *ALPPS* Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy, *TSH* Two-Stage Hepatectomy, *SMD* standardized mean difference, *RR* risk ratio, *CI* confidence interval, *SD* standard deviation.

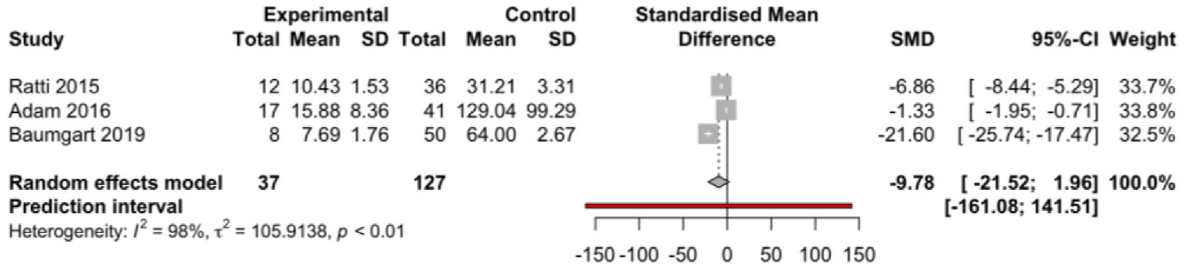
included studies, there was only one RCT [35] and the remainder were retrospective studies [36–39]. The median sample size in the ALPPS group was 17 (range 8–48) and 41 (range 36–50) in the TSH group. No significant differences were found in age, gender, or ASA score between the ALPPS and TSH groups, although one study reported higher body mass index in the TSH group (26.4 *vs* 24.9; $p = 0.023$)[35]. Regarding tumor characteristics, no significant differences were found in the location, T-stage or N-stage of the primary tumor, presence of synchronous/metachronous metastases, number and size of liver lesions, or presence of extrahepatic disease between ALPPS and TSH groups. At least seventy-five percent of patients included in the studies received preoperative chemotherapy, with a median of 6 preoperative chemotherapy cycles (range 2–37) in both groups [36–38]. Heterogeneity between studies was found when comparing preoperative chemotherapy schemes, differing among oxaliplatin, irinotecan or capecitabine, and biologic agents [35–38]. Response to chemotherapy was assessed using the Response Evaluation Criteria In Solid Tumors (RECIST) before first-stage hepatectomy was performed. Progression rates ranged from 0% to 11% [35,37,38]. Only one study[37] reported interval chemotherapy between first and second hepatectomy in the TSH group.

3.2. Perioperative outcomes

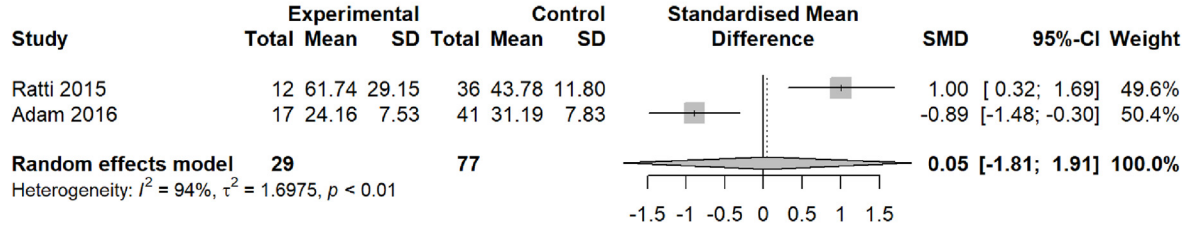
All of the studies included in the meta-analysis reported intra- and postoperative outcomes *(*Table 2b*)* [35–39].

The analysis of operative time in stage 1 hepatectomy showed no significant differences between the two groups [36,37] (SMD 1.21, 95% CI -0.13–2.55), while significant differences were

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 20, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.



A Meta-analysis of studies on time interval between first and second hepatectomy of patients undergoing ALPPS vs TSH.



B Meta-analysis of studies on %FLR increase of patients undergoing ALPPS vs TSH.

Fig. 3. Forest plot comparing volumetric outcomes of ALPPS versus TSH. **A** Time interval between first and second hepatectomy; **B** Percentage of future liver remnant (%FLR) increase. *ALPPS* Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy, *TSH* Two-Stage Hepatectomy, *SMD* standardized mean difference, *CI* confidence interval, *SD* standard deviation.

observed between techniques in terms of lower surgery duration for patients undergoing stage 2 hepatectomy in ALPPS group (SMD -1.99, 95% CI -3.78 to −0.20), although heterogeneity levels between studies were substantial (I^2 = 91%, p < 0.01). Regarding length of stay, significant differences were also observed between the two groups in favor of the THS group (SMD 1.13, 95% CI 0.62–1.65, I^2 = 0%, p = 0.47). Only two studies evaluated the intraoperative red blood cell transfusion [36,37]; in stage 1, significant differences were observed between groups in detriment of the ALPPS group (RR 6.78, 95% CI 2.30–19.94, I^2 = 0%, p = 0.57), whilst no differences were observed in stage 2 hepatectomy (RR 1.80, 95% CI 0.74–4.38, I^2 = 18%, p = 0.27). A meta-analysis of the two studies [36,37] reporting minor complications showed benefit in the TSH group (RR 3.19, 95% CI 1.81–5.65, I^2 = 0%, p = 0.47). Likewise, differences were observed between techniques in terms of lower major complications for patients undergoing TSH (RR 1.46, 95% CI 1.04–2.06, I^2 = 0%, p = 0.71). Nevertheless, the five studies included [35–39] reported perioperative mortality data (Table 2b), with no significant differences observed between groups (RR 1.53, 95% CI 0.64–3.62, I^2 = 0%, p = 0.64). However, only one study [36] reported higher mortality rate in the ALPSS group after second hepatectomy (8.3% *vs* 2.9%; p = 0.041). Completion of hepatectomy was reported in four studies [35–37,39], showing a benefit in favor of the ALPPS group (RR 1.32, 95% CI 1.09–1.61), although heterogeneity among studies were considerable (I^2 = 85%, p < 0.01). Furthermore, a significant difference was observed in terms of R0 resection, in favor of the ALPPS technique (RR 1.61, 95% CI 1.13–2.30, I^2 = 40%, p = 0.19), in the three studies included [35,37,39]. A meta-analysis of the included studies is shown in Fig. 2.

3.3. Volumetric outcomes

Only three studies reported on time interval between first and second hepatectomy [36,37,39], with no significant differences between the two groups (SMD -9.78, 95% CI -21.52–1.96), although heterogeneity levels among studies were considerable (I^2 = 98%, p < 0.01).

The analysis of the percentage of FLR increase showed no significant differences between the two groups (SMD 0.05, 95% CI -1.81–1.91, I^2 = 94%, p < 0.01). A meta-analysis of the included studies is shown in Fig. 3.

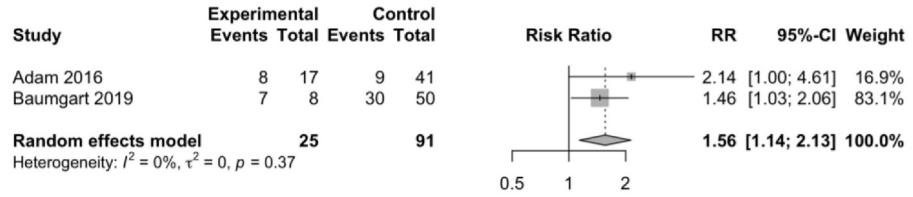
3.4. Oncological outcomes

Four studies separately analyzed postoperative local recurrence, OS and DFS [36–39]. Meta-analysis of the two studies [37,39] reporting local recurrence confirmed a lower recurrence rate in the TSH group (RR 1.56, 95% CI 1.14–2.13, I^2 = 0%, p = 0.37). Nevertheless, no significant differences were achieved between the two groups in terms of OS (RR 0.93, 95% CI 0.68–1.27, I^2 = 52%, p = 0.10) and DFS (RR 1.08, 95% CI 0.47–2.49, I^2 = 54%, p = 0.11), respectively. Only one study reported a significantly lower 2-year OS after diagnosis of liver metastases in the ALPPS group (72% *vs* 95%; p = 0.017)[37]. A meta-analysis of the included studies is shown in Fig. 4.

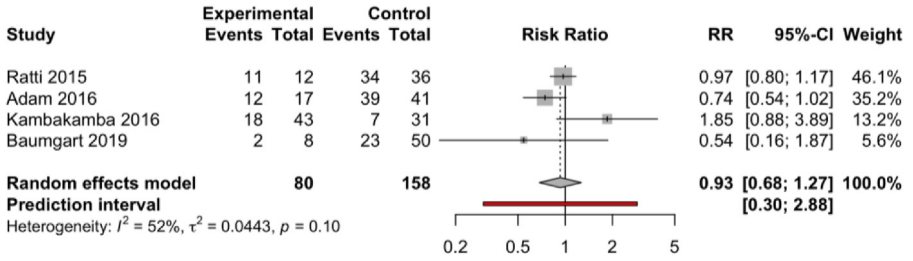
4. Discussion

Few reports have contributed to the literature comparing the benefit of ALPPS versus TSH for initially unresectable CRLM. Despite first concerns about the safety of ALPPS, morbidity rates related to the first and second hepatectomies were subsequently proven to be comparable to those of TSH [27]. However, the rapid hypertrophy of the FLR [40] and the increased resectability rate [35] achieved with ALPPS technique compared to TSH, does not necessarily entail improved oncological outcomes. Therefore, definitive and sustainable conclusions from prospective studies comparing both ALPPS

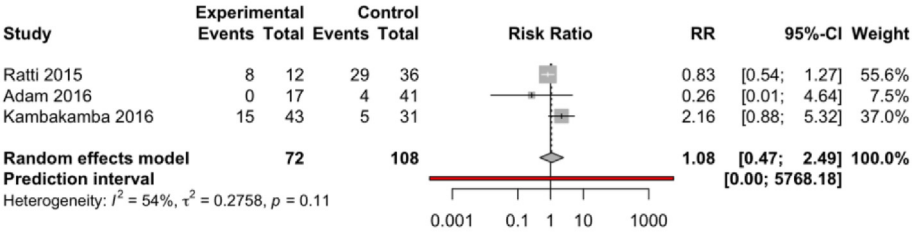
Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 20, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.



A Meta-analysis of studies on local recurrence of patients undergoing ALPPS vs TSH.



B Meta-analysis of studies on overall survival of patients undergoing ALPPS vs TSH.



C Meta-analysis of studies on disease-free survival of patients undergoing ALPPS vs TSH.

Fig. 4. Forest plot comparing oncological outcomes of ALPPS versus TSH. **A** Local recurrence; **B** Overall survival; ***C*** Disease-free survival; *ALPPS* Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy, *TSH* Two-Stage Hepatectomy, *SMD* standardized mean difference, *CI* confidence interval, *SD* standard deviation.

technique and TSH in the setting of initially unresectable CRLM are missing. Accordingly, by including the evidence available to date, this meta-analysis is one of the first to assess whether there are perioperative benefits that lead to improvements in oncological outcomes regarding CRLM of one technique with respect to another.

Concerning morbidity and mortality, when considering both stages, major complications reported for ALPPS ranged from 13%[41]–64% [28]. Mortality after stage two hepatectomy dropped from the initially reported rate of 12% to the actual value of 7% [20,21]. Similar related morbidity and mortality rates were described for conventional TSH [28,42]. It is convenient to highlight that most of the studies comparing ALPPS and TSH comprised patients with a wide variety of malignancies. In the present analysis, minor and major complications were more frequent in the ALPPS group compared to the TSH group (RR 3.19, 95% CI 1.81–5.65 and RR 1.46, 95% CI 1.04–2.06, respectively). However, no significant differences were observed regarding perioperative mortality (RR 1.53, 95% CI 0.64–3.62, $I^2 = 0\%$, $p = 0.64$). Nevertheless, it is remarkable that only one study [38] reported PHLF according to the definition proposed by the International Study Group of Liver Surgery (ISGLS) [43]. Therefore, the real incidence of this severe complication could have been biased. Similarly, none of the included studies described significant differences in mortality rate between the ALPPS and TSH groups.

Drug-specific histological changes, such as steatosis, steatohepatitis, sinusoidal obstructive syndrome or biliary sclerosis, have been described as hepatotoxic effects of preoperative chemotherapy and can lead to increased morbidity and mortality after resection because of liver dysfunction [44]. The effects of these toxic effects on growth of the FLR are controversial [45,46]. Although large degrees of heterogeneity have been reported regarding chemotherapy regimens, the current analysis reported no drug-specific histopathological changes in the underlying liver parenchyma after resection or differences in the percentage of FLR growth between TSH and ALPPS groups. Thus, the roles of hepatotoxic effects derived from chemotherapy on PHLF or liver regeneration are particularly complex to assess.

As it is known, one of the main benefits of ALPPS technique is the rapid regeneration of FLR compared to conventional TSH. The reported kinetic growth rates were almost tenfold higher for ALPPS than with TSH [41,47,48], although some authors described more immature hepatocytes in the FLR of patients who underwent ALPPS [42]. Despite this, PHLF rates in the aforementioned study [38] were not significantly higher in the ALPPS group after completion of the second hepatectomy; thus, by applying the appropriate concepts, future clinical trials should evaluate the thought that volume does not equal function.

A considerable finding, and one of the historical drawbacks of conventional TSH, is the percentage of patients who do not proceed

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 20, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

to second hepatectomy because of tumor progression or insufficient FLR hypertrophy; the reported dropout rates vary from 8 to 41% [49–51]. It is a matter of debate whether this reflects a failure of the surgical strategy or anticipation of poor oncological outcomes in patients with more aggressive tumor biology. In fact, some authors have argued that a slightly longer interstage time interval to volumetric control in ALPPS may be beneficial for the patient, thus allowing tumor biology to be expressed and avoiding futile interventions in terms of DFS and OS[22,] [50]. In a recent meta-analysis, Moris et al. [52] reported no difference in DFS despite higher resectability rate in ALPPS compared to TSH. Furthermore, although higher resection rates have been reported favoring ALPPS against TSH [41], no differences in radicality (R0 resection) were reported in any of the articles included in the analysis.

Impact on long-term survival deserves a more detailed study. Contradictory findings have been reported regarding oncological outcomes of patients undergoing ALPPS or TSH for CRLM. Published data concerning OS and DFS between both strategies may be highly biased by the consideration of different malignancies clustered under a common entity [22–28,40,42,53,54]. The only RCT published in this field concluded that the rate of early tumor recurrence is similar between techniques after 12 months of follow-up when radical resection has been achieved (54.5% vs 53.8% in the TSH and ALPPS groups, respectively) [55]. More recently, survival analysis of the same RCT demonstrated that patients randomized to ALPPS had a significantly longer survival than those randomized to TSH (46 *vs* 26 months, respectively) [56].

There are a number of limitations to this systematic review and meta-analysis. Although comparative publications were included, the majority were retrospective studies with small sample sizes conducted in single centers. Besides, only five articles were considered for eligibility; thus, considerable heterogeneity was observed among them. Although the methodological quality of the studies was assessed as good, the level of evidence was low, mainly because of the retrospective design of the studies. When comparing conventional TSH and ALPPS, homogeneity between groups seems impossible to achieve unless selection criteria for patients and indications, preoperative chemotherapy schemes, and definitions of surgical techniques and postoperative complications are standardized. An additional source of bias is that there was no blinded evaluation of objective endpoints in any of the studies included; ergo, although the quality of included studies was variable, this review represents the state of the literature published to date. Taking into consideration that the oncological outcomes, more than feasibility or even resection rate, must be the end-point of every oncological surgical technique, factors affecting OS or recurrence must be taken into account when comparing groups. Therefore, location, TNM staging, and K-ras mutations of primary tumors should be assessed, as should the presence of associated less invasive procedures such as radiofrequency ablation. Lastly, duration of follow-up in the included studies might imply lack of information regarding postoperative and long-term oncological outcomes from several cohorts.

In conclusion, this comprehensive meta-analysis suggests that TSH seems to have better postoperative adverse events in terms or morbidity; however, both ALPPS and conventional TSH for initially unresectable CRLM appear to have comparable perioperative mortality rates at experienced centers. Although promising, the authors conclude by recommending a cautious embrace of these assessments, recognizing both the inherent limitations and the demonstrated heterogeneity among studies. Despite the fact that higher resection rates have been reported with ALPPS, no differences in radicality were found between both techniques. No definitive conclusions in terms of OS and DFS can be drawn from the results. Moreover, further high-quality and prospective randomized and multicenter studies encompassing all prognostic factors related to oncological outcomes in CRLM are needed to assess the role of these techniques and clarify the potential benefit of one technique over the other in the short and long-term before either ALPPS or TSH can be recommended as the standard of care for initially unresectable CRLM.

CRediT author statement

Pablo Granero Castro, Study concepts, Manuscript preparation. Tamara Díaz Vico, Study design and interpretation, Statistical analysis, Manuscript preparation. Laura Alcover Navarro, Data acquisition, Data curation. Aida Suárez Sánchez, Data acquisition, Data curation. Eva Montalvá, Quality control of data and algorithms. Javier Maupoey, Quality control of data and algorithms. Luka Mihic Góngora, Manuscript editing. Nuria Truán Alonso, Manuscript review. Ignacio González-Pinto Arrillaga, Manuscript review. José Electro Granero Trancón, Manuscript review. Approval of the version to be published: All authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgments

The authors thank Patricio Suárez Gil and Valeria Rolle Sóñora from the Department of Biostatistics and Epidemiology at the Health Research Institute of the Principality of Asturias (ISPA).

References

[1] House MG, Ito H, Gönen M, Fong Y, Allen PJ, De Matteo RP, et al. Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. J Am Coll Surg 2010;210:744–52.
[2] Hackl C, Neumann P, Gerken M, Loss M, Klinkhammer-Schalke M, Schlitt HJ. Treatment of colorectal liver metastases in Germany: a ten-year population-based analysis of 5772 cases of primary colorectal adenocarcinoma. BMC Cancer 2014;14:810.
[3] Ye LC, Liu TS, Ren L, Wei Y, Zhu DX, Zai SY, et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. J Clin Oncol 2013;31:1931–8.
[4] Folprecht G, Gruenberger T, Bechstein W, Raab HR, Weitz J, Lordick F, et al. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). Ann Oncol 2014;25:1018–25.
[5] Köhne CH, Poston G, Folprecht G, Ciardiello F, Ronga P, Beier F, et al. FOLFIRI plus cetuximab in patients with liver-limited or nonliver-limited RAS wild-type metastatic colorectal cancer: a retrospective subgroup analysis of the CRYSTAL study. Eur J Surg Oncol 2016;42:1540–7.
[6] Uetake H, Yasuno M, Ishiguro M, Kameoka S, Shimada Y, Takahashi K, et al. A multicenter phase II trial of mFOLFOX6 plus bevacizumab to treat liver-only metastases of colorectal cancer that are unsuitable for upfront resection (TRICC0808). Ann Surg Oncol 2015;22:908–15.
[7] Rouyer M, Smith D, Laurent C, Becouarn Y, Guimbaud R, Michel P, et al. ETNA study group. Secondary metastases resection after bevacizumab plus irinotecan-based chemotherapy in first-line therapy of metastatic colorectal cancer in a real-life setting: results of the ETNA cohort. Targeted Oncol 2016;11:83–92.
[8] Modest DP, Denecke T, Pratschke J, Ricard I, Lang H, Bemelmans M, et al. Surgical treatment options following chemotherapy plus cetuximab or bevacizumab in metastatic colorectal cancer-central evaluation of FIRE-3. Eur J Cancer 2018;88:77–86.
[9] Jones RP, Hamann S, Malik HZ, Fenwick SW, Poston GJ, Folprecht G. Defined criteria for resectability improves rates of secondary resection after systemic therapy for liver limited metastatic colorectal cancer. Eur J Cancer 2014;50:1590–601.

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 20, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

[10] Jones RP, Vauthey JN, Adam R, Rees M, Berry D, Jackson R, et al. Effect of specialist decision-making on treatment strategies for colorectal liver metastases. Br J Surg 2012;99:1263–9.
[11] Bismuth H, Adam R, Lévi F, Farabos C, Waechter F, Castaing D, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg 1996;224:509–20.
[12] Makuuchi M, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunvén P, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery 1990;107:521–7.
[13] Jaeck D, Oussoultzoglou E, Rosso E, Greget M, Weber JC, Bachellier P. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. Ann Surg 2004;240:1037–49.
[14] Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: a planned strategy to treat irresectable liver tumors. Ann Surg 2000;232:777–85.
[15] Brouquet A, Abdalla EK, Kopetz S, Garrett CR, Overman MJ, Eng C, et al. High survival rate after two-stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. J Clin Oncol 2011;29:1083–90.
[16] Pandanaboyana S, Bell R, Hidalgo E, Toogood G, Prasad KR, Bartlett A, et al. A systematic review and metaanalysis of portal vein ligation versus portal vein embolization for elective liver resection. Surgery 2015;157:690–8.
[17] Simoneau E, Hassanain M, Shaheen M, Aljiffry M, Molla N, Chaudhury P, et al. Portal vein embolization and its effect on tumour progression for colorectal cancer liver metastases. Br J Surg 2015;102:1240–9.
[18] Giuliante F, Ardito F, Ferrero A, Aldrighetti L, Ercolani G, Grande G, et al. Tumor progression during preoperative chemotherapy predicts failure to complete 2-stage hepatectomy for colorectal liver metastases: results of an Italian multicenter analysis of 130 patients. J Am Coll Surg 2014;219:285–94.
[19] Baumgart J, Lang S, Lang H. A new method for induction of liver hypertrophy prior to right trisectionectomy: a report of three cases. HPB 2011;13:1–145.
[20] Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 2012;255:405–14.
[21] Schadde E, Ardiles V, Robles-Campos R, Malago M, Machado M, Hernandez-Alejandro R, et al., ALPPS Registry group. Early survival and safety of ALPPS: first report of the International ALPPS Registry. Ann Surg 2014;260:829–36.
[22] Raptis DA, Linecker M, Kambakamba P, Tschuor C, Müller PC, Hadjittofi C, et al. Defining benchmark outcomes for ALPPS. Ann Surg 2019;270:835–41.
[23] Grąt M, Hołówko W, Lewandowski Z, Kornasiewicz O, Barski K, Skalski M, et al. Early post-operative prediction of morbidity and mortality after a major liver resection for colorectal metastases. HPB 2013;15:352–8.
[24] Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C, et al. European surgical outcomes study (EuSOS) group for the trials groups of the European society of intensive care medicine and the European society of anaesthesiology. Mortality after surgery in europe: a 7 day cohort study. Lancet 2012;380:1059–65.
[25] Schadde E, Ardiles V, Slankamenac K, Tschuor C, Sergeant G, Amacker N, et al. 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 2014;38:1510–9.
[26] Croome KP, Hernandez-Alejandro R, Parker M, Heimbach J, Rosen C, Nagorney DM. Is the liver kinetic growth rate in ALPPS unprecedented when compared with PVE and living donor liver transplant? A multicentre analysis. HPB 2015;17:477–84.
[27] Tanaka K, Matsuo K, Murakami T, Kawaguchi D, Hiroshima Y, Koda K, et al. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): short-term outcome, functional changes in the future liver remnant, and tumor growth activity. Eur J Surg Oncol 2015;41:506–12.
[28] Shindoh J, Vauthey JN, Zimmitti G, Curley SA, Huang SY, Mahvash A, et al. 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 2013;217:126–33.
[29] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al., PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRIMSA-P) 2015 statement. Syst Rev 2015;4:1.
[30] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Contr Clin Trials 1996;17:1–12.
[31] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, ON, Canada: Ottawa Hospital Research Institute; 2000.
[32] Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020. URL, https://www.R-project.org/.
[33] Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Base Ment Health 2019;22:153–60.
[34] Prospero international prospective register of systematic reviews. Available online: https://www.crd.york.ac.uk/PROSPERO/. [Accessed 19 February 2019]. registered on 24 April 2019.
[35] Sandström P, Rosok BI, Sparrelid E, Larsen PN, Larsson AL, Lindell G, et al. ALPPS improves resectability compared with conventional two-staged hepatectomy in patients with advanced colorectal liver metastases. Results from a Scandinavian multicenter randomized controlled trial (LIGRO trial). Ann Surg 2018;267:833–40.
[36] Ratti F, Schadde E, Masetti M, Massani M, Zanello M, Serenari M, et al. 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 2015;22:1933–42.
[37] Adam R, Imai K, Castro Benitez C, Allard MA, Vibert E, Sa Cunha A, et al. Outcome after associating liver partition and portal vein ligation for staged hepatectomy and conventional two-stage hepatectomy for colorectal liver metastases. Br J Surg 2016;103:1521–9.
[38] Kambakamba P, Linecker M, Alvarez FA, Samaras P, Reiner CS, Raptis DA, et al. Short chemotherapy-free interval improves oncological outcome in patients undergoing two-stage hepatectomy for colorectal liver metastases. Ann Surg Oncol 2016;23:3915–23.
[39] Baumgart J, Jungmann F, Bartsch F, Kloth M, Mittler J, Heinrich S, et al. Two-staged hepatectomy and ALPPS for advanced bilateral liver metastases: a tailored approach balancing risk and outcome. J Gastrointest Surg 2019;23:2391–400.
[40] Chia DKA, Yeo Z, Loh SEK, Iyer SG, Bonney GK, Madhavan K, et al. Greater hypertrophy can be achieved with associating liver partition with portal vein ligation for staged hepatectomy compared to conventional staged hepatectomy, but with a higher price to pay? Am J Surg 2018;215:131–7.
[41] Matsuo K, Murakami T, Kawaguchi D, Hiroshima Y, Koda K, Yamazaki K, et al. Histologic features after surgery associating liver partition and portal vein ligation for staged hepatectomy versus those after hepatectomy with portal vein embolization. Surgery 2016;159:1289–98.
[42] Abulkhir A, Limongelli P, Healey A, Damrah O, Tait P, Jackson J, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. Ann Surg 2008;247:49–57.
[43] Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the international study group of liver surgery (ISGLS). Surgery 2011;149:713–24.
[44] Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg 2007;94:274–86.
[45] Kremer M, Manzini G, Hristov B, Polychronidis G, Mokry T, Sommer CM, et al. 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 2015;221:717–28.
[46] Hasselgren K, Malago M, Vyas S, Campos RR, Brusadin R, Linecker M, et al. Neoadjuvant chemotherapy does not affect future liver remnant growth and outcomes of associating liver partition and portal vein ligation for staged hepatectomy. Surgery 2017;161:1255–65.
[47] Croome KP, Hernandez-Alejandro R, Parker M, Heimbach J, Rosen C, Nagorney DM. Is the liver kinetic growth rate in ALPPS unprecedented when compared with PVE and living donor liver transplant? A multicentre analysis. HPB 2015;17:477–84.
[48] Kambakamba P, Linecker M, Schneider M, Reiner CS, Nguyen-Kim TDL, Limani P, et al. Impact of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) on growth of colorectal liver metastases. Surgery 2018;163:311–7.
[49] Lam VW, Laurence JM, Johnston E, Hollands MJ, Pleass HC, Richardson AJ. A systematic review of two-stage hepatectomy in patients with initially unresectable colorectal liver metastases. HPB 2013;15:483–91.
[50] Imai K, Benitez CC, Allard MA, Vibert E, Cunha AS, Cherqui D, et al. Failure to achieve a 2-stage hepatectomy for colorectal liver metastases: how to prevent it? Ann Surg 2015;262:772–8.
[51] Aloia TA, Vauthey JN. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): what is gained and what is lost? Ann Surg 2012;256:e9. ; author reply e16–e19.
[52] Moris D, Ronnekleiv-Kelly S, Kostakis ID, Tsilimigras DI, Beal EW, Papalampros A, et al. 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 2018;42:806–15.
[53] Knoefel WT, Gabor I, Rehders A, Alexander A, Krausch M, Schulte J, et al. In situ liver transection with portal vein ligation for rapid growth of the future liver remnant in two-stage liver resection. Br J Surg 2013;100:388–94.
[54] Maupoey Ibáñez J, Montalvá Orón EM, Robledo Boscà, et al. From conventional two-stage hepatectomy to ALPPS: fifteen years of experience in a hepatobiliary surgery unit. Hepatobiliary Pancreat Dis Int 2021 Dec;20(6):542–50.
[55] Rosok BI, Host-Brunsell T, Brudvik KW, Carling U, Dorenberg E, Björnsson B, et al. 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 2019;21:1017–23.
[56] Hasselgren K, Røsok BI, Larsen PN, Sparrelid E, Lindell G, Schultz NA, et al. ALPPS improves survival compared with TSH in patients affected of CRLM: survival analysis from the randomized controlled trial LIGRO. Ann Surg 2021 Mar 1;273(3):442–8.

Descargado para Lucia Angulo (lu.maru26@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 20, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.