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RH Developed the concepts, organized the effort to prepare the manuscript, and edited the manuscript. LR developed the concepts, wrote the manuscript and developed the figures and tables. RA, BB, OT, and AS Developed the concepts and provided critical edits to the manuscript, and All authors approve of the final version of this manuscript.

Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) Procedure for Colorectal Liver Metastasis

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Introduction:

The remarkable regenerative capacity of the liver is unique amongst solid organs, and has captivated the human imagination since antiquity: in Greek mythology the Titan Prometheus is chained for eternity, sentenced to have his liver repeatedly devoured by an eagle, only to have it regrow in place for repeated torment. The ability to leverage the organ's regenerative capacity has facilitated progressively more aggressive approaches to previously considered unresectable hepatic tumors. In the management of colorectal liver metastases (CRLM) in particular, the paradigm has shifted from previously unresectable criteria, to the standard-of-care being surgical resection of metastases as long as there remains sufficient future liver remnant (FLR), typically 20-30% of the healthy native liver [1]. Over the last two decades advances in liver surgery have pushed the boundary of resectability by incorporating vascular modulation such as portal venous ligation (PVL), embolization (PVE), and two-stage hepatectomies (TSH) to clear the FLR of invasive disease.

In 2007 a German surgeon, Prof. HJ Schlitt serendipitously discovered the synergistic effect of parenchymal transection and deportalization, which resulted in accelerated hypertrophy of the remnant liver: During the course of a right trisectionectomy for perihilar cholangiocarcinoma, Prof. Schlitt aborted the procedure after having ligated the right portal vein due to concern for insufficient FLR. Astoundingly, just a week after this procedure, the left-lateral section was discovered to have nearly doubled in size. This allowed the completion hepatectomy just eight days after the initial surgery. This concept of parenchymal transection and deportalization became known as Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) [2]. The inaugural description of accumulated experience with ALPPS in German clinics was presented four years later at the congress of the European African-Hepato-Pancreato-Biliary Association to a captivated audience in Capetown, South Africa , and the first 25 cases were published a year later [3]. At that time the HPB community reverberated with intrigue and boisterous enthusiasm as well as skepticism [4–6]. It is no

overstatement to suggest that in the decade since first performed, ALPPS remains one of the most continuously evolving and controversial HPB procedures in the literature, with a distinct demarcation on either side of the Atlantic [7]. Yet out of the nascent first descriptions and rapid adoption, robust data has begun to accumulate helping to guide the experienced liver surgeon on *when* and *if* to utilize ALPPS. Here the evolution of ALPPS is reviewed, and as the procedure enters its thirteenth year of existence, we highlight critical lessons with a focus on the use of ALPPS for CRLM.

Early adoption, modifications, and refinement of indications:

Soon after the first description of ALPPS, the procedure was adopted quickly, simultaneously being employed for a number of indications [8–10]. As a result the first described series of ALPPS were accompanied by alarming rates of perioperative morbidity and 90 day mortalities as high as 48% depending on the indication [9–11]. Not surprisingly there was a recoil against the procedure, due to what some called “innovation for innovation’s sake” [12]. Indeed, a close evaluation of ALPPS cases compiled in the international registry found a misuse of the procedure, with an unacceptably high number of cases being performed in patients who likely did not have an indication for a two-stage procedure [13]. It was readily apparent that ALPPS was similar to a zero-sum game; improved resectability and hypertrophy had to be counterbalanced with increased perioperative morbidity, and a careful assessment during interstage to decide if and when to proceed to completion resection [14–16].

In order to address these early poor outcomes, surgeons developed modifications to the ALPPS procedure, attempting to mitigate a prolonged, invasive stage I procedure [17,18]. To this goal *partial* ALPPS was developed, offering comparable hypertrophic benefit to the classical ALPPS when transection occurs through at least 50% of the liver parenchyma, and with considerably less morbidity and minimal perioperative mortality [19,20]. Similarly, *mini* ALPPS combines a limited parenchymal transection paradigm, with minimal dissection of the porta hepatis by utilization of an intraoperative PVE [17]. One step beyond, *tourniquet* ALPPS spares

parenchymal transection altogether, and instead drives hepatocyte stimulation through application of a vertical tourniquet through the future transection plane [21,22]. When combined with PVE, *tourniquet* ALPPS has been successfully applied to a variety of tumors including primary liver malignancies [23].

Additionally, descriptions of minimally invasive approaches to stage I through laparoscopic or robotic assisted procedures have been reported [24–26]. Encouragingly, the experience from São Paulo and others has demonstrated that laparoscopic ALPPS can be performed with excellent perioperative morbidity, mortality, and improved length-of-stay compared to classical ALPPS [27,28].

Anatomically, critical pitfalls in respecting hepatic inflow and outflow have amassed; preservation of the middle hepatic vein and section 3 venous drainage to maintain adequate outflow, careful interrogation of aberrant hepatic arterial anatomy, and careful interrogation of biliary anatomy to prevent injury to the segmental bile ducts during dissection, which can result in bile leaks and interstage sepsis [29].

Perhaps the greatest advances in mitigating poor outcomes from the ALPPS procedure has been the improvement in preoperative and interstage decision making. When first inaugurated, ALPPS was widely applied to various histologies, including intrahepatic cholangiocarcinoma (CCA), perihilar CCA, hepatocellular carcinoma, and CRLM, yet with little consideration for underlying liver disease, portal hypertension, or chemotherapy induced hepatic injury.

The most common cause of postoperative mortality following ALPPS is post-stage II hepatic failure [30] To guide decision making prior to stage II, risk models have been developed and validated [31,32]. During interstage, an elevation in serum creatinine or total bilirubin have been linked to hepatic failure and mortality. Similarly post-stage I complications of Clavien-Dindo class 3b or higher and an elevated pre-stage I risk score increase the risk of post-stage II mortality [33]. The available pre-stage I and pre-stage II risk scores should be utilized by all

practitioners of ALPPS in order to guide improvement in surgical quality and refinement of the risk scoring with added experience.

Mechanisms of Hypertrophy, Assessment of Hepatic Function, and Effects on Oncologic Outcome:

Dissimilar from ALPPS, following PVE it has been shown that hepatic volumetric growth may in some cases lag behind increased hepatic function [34]. Furthermore, in both ALPPS and PVE hepatic volume increase has been demonstrated to be a poor surrogate of increased hepatic function [35,36]. Mechanistically, preclinical rodent models of ALPPS have elucidated soluble factors IL6, TNFα and transcriptional regulation of phospho-STAT3 and YAP amongst others as drivers of hypertrophy with limited correlation with resected human tissue [37,38]. However, definitive mechanisms of what separated ALPPS from PVE alone remain elusive, and basic science in understanding the cellular mechanisms are an unmet need in the literature [29]. Fortunately, in the absence of biomarkers, hepatic scintigraphy has emerged as an adjunct for assessing adequate liver function. Serenari et al. recently demonstrated the use of single photon emission computed tomography (SPECT) utilizing ^{99mTc}-mebrofenin can reliably segregate patients who demonstrate adequate hepatic function within the FLR (>15% of total counts) from those at risk of post-stage II hepatic failure [39]. Coupled with established risk scoring, SPECT imaging may aid in decision making regarding safety of undertaking stage II.

Some opponents of the ALPPS approach raise the concern of increased oncologic virulence by unleashing the rapid hypertrophy observed after ALPPS. Indeed some early reports highlighted rapid recurrence in cohorts of patients undergoing ALPPS [40]. However human observations and preclinical models have failed to demonstrate any difference in tumor stimulation between ALPPS or PVL/PVE [41]. Furthermore, histologic and immunohistochemical analyses of resected specimens following ALPPS and partial hepatectomy demonstrated no statistically significant difference in vascular invasion, proliferation, apoptosis, or recruitment of cancer associated fibroblasts [42]. While these studies remain limited by a lack of understanding of hypertrophic pathways and potential synergy across disparate oncologic drivers for different

tumor histologies, to date no data has demonstrated that ALPPS uncovers more aggressive tumor biology compared to alternatives such as PVE.

ALPPS for CRLM:

Colorectal cancer is the third most common malignancy worldwide, and 50% of patients present with or eventually develop hepatic metastases. Robust data has supported the oncologic benefit of CRLM resection and centers have even begun to explore the benefit of local treatment through total hepatectomy and transplantation in selected patients [43,44]. Analysis of the international ALPPS registry has shown CRLM as the best indication for applying ALPPS in patients with insufficient FLR [13]. Not surprisingly, this population is typically younger, has normal portal venous pressure and without underlying liver disease. However, careful multidisciplinary decision making, patient selection, and neoadjuvant therapeutic approach must be employed to navigate patients with borderline resectable CRLM to curative intent resection.

Given the opportunity to downstage CRLM with increasingly more effective systemic regimens, patients should be given the trial of neoadjuvant chemotherapy in an attempt to preserve hepatic parenchyma, understand the tumor's biology, and potentially obviate the need for more radical surgery [45]. Furthermore, patients who progress radiographically or biochemically while on systemic therapy portend a poor prognosis despite resection, with a propensity for recurrence after surgery [46]. Extensive two stage procedures in this population should be approached with caution if not avoided. Most patients who present with liver-confined stage IV CRC do so synchronously with a primary lesion [47]. Patients who present with symptomatic primary lesions, either due to hemorrhage or obstruction should have the primary disease addressed. Similarly, patients with obstructing rectal adenocarcinoma may be initially treated with combination multimodal therapy for control of primary disease. However, a liver-first approach, after neoadjuvant therapy, in the case of asymptomatic primary lesions can yield improved outcomes by avoiding post-colectomy complications which obviate systemic therapy

and result in loss of resectability for hepatic disease compared to colon-first approach [48]. A third alternative is synchronous resection, however, given the potential postoperative morbidity and increased mortality associated with colectomy and hepatectomy, it is not advisable to pursue synchronous primary resection and ALPPS [49,50].

A review of the International ALPPS Registry shows perioperative morbidity and mortality to be in keeping with other major hepatectomies when performed for CRLM [30]. Furthermore, reports from high volume centers demonstrate a 3-year survival of 50% and disease-free-survival of 13%, and importantly quality-of-life metrics in patients who underwent ALPPS were similar to the general population, demonstrating the ability of ALPPS to deliver disease control while returning patients to meaningful daily lives [51]. Still, early comparisons between ALPPS and TSH yielded discordant conclusions with some reports demonstrating worse intermediate survival with ALPPS compared to TSH, while others demonstrating parity between the two approaches [22,52,53]. More recently, completion of the first randomized control trial for patients with unresectable CRLM and FLR<30% has allowed the most adequate head-to-head comparison to date.

The LIGRO trial was a scandanavian based randomized clinical trial which enrolled 100 patients to ALPPS or TSH with the option of rescue ALPPS in the PVE group. The primary end-point of the study was to evaluate resectability following vascular modulation in patients with colorectal liver metastases and insufficient future liver remnant. The first report from the trial demonstrated a positive result, with resection rates in the ALPPS arm compared to the PVE arm of 92% and 57% respectively ($p<0.0001$) [54] (Figure 1). Additionally, of the 21 patients that failed to attain sufficient hypertrophy following PVE, 57% were able to undergo salvage ALPPS and became resectable.

It is important to note that the PVE methodology was not standardized across institutions, and the 57% resectability following PVE is low compared to contemporary reports which have demonstrated rates above 85% following PVE [55,56]. Nonetheless, postoperative

morbi-mortality was similar between the two groups, and there was a trend towards improved R0 resection rate (R0 RR) in the ALPPS group compared to PVE [R0 RR: ALPPS 77% (34/44) vs PVE 57% (16/28) P = 0.11] [54]. This is in keeping with results from the European REBIRTH RCT, which demonstrated a 92.3% vs. 66.6% resection rate following radio-frequency ablation ALPPS and PVE respectively in patients with primary or secondary liver malignancy and insufficient FLR [57]. Furthermore, recurrence in the LIGRO trial after ALPPS was similar to TSH, with 7/13 patients who underwent ALPPS and 6/11 patients who underwent PVE and TSH experiencing recurrence of disease within a year [58].

The most interesting result of the LIGRO trial was the finding of improved survival in the ALPPS group compared to the TSH group. With a median follow up of 36 months, ALPPS demonstrated an estimated median survival of 46 months compared to just 26 months for patients randomized to TSH (p=0.028) (Figure 1) [59]. Furthermore, at the first postoperative follow-up 77% of patients in the ALPPS group were assessed as tumor-free compared to 57% of patients randomized to the TSH group (p.0.028) [59]. Taken together, these results provide the strongest evidence and support the application of ALPPS for patients with CRLM.

Conclusions:

ALPPS remains a critical tool in the armamentarium liver surgeons which must be deployed with careful consideration and with the application of evidenced based risk-stratification to ensure the best outcome for patients. Perioperative morbi-mortality have improved to be comparable with other major hepatectomy approaches such as TSH, and a recently reported randomized trial demonstrated improved survival for patients treated with ALPPS compared to TSH. The LIGRO trial, while the strongest evidence to date in support of ALPPS for surgical control of colorectal liver metastases with insufficient future liver remnant, should be replicated in future clinical trials in order to validate these findings in other indications and amongst diverse patient populations and healthcare delivery systems.

Summary:

- ALPPS has demonstrated excellent ability to achieve resectability compared to PVE and TSH in patients with CRLM and insufficient FLR.
- Outcomes with ALPPS for CRLM have improved and are comparable to other major hepatectomies.
- There is no evidence that the enhanced hypertrophy generated by ALPPS is oncologically inferior to techniques such as PVE or PVL.
- ALPPS is a single tool in a broader armamentarium that should not be overused or misused.
- Patient's CRC biology should be considered when considering surgical intervention; poor tumor biology is rarely defeated by herculean surgery.

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To the Editors and Reviewers,

Thank you for the opportunity to revise our work detailing recent advances utilizing the ALPPS technique for CRLM. We have addressed all comments and suggestions and present the revised manuscript. Steps taken to address the concerns follow point by point in **Bold**.

Respectfully,

The authors

Senior Editor: The review was reviewed by 2 expert reviewers and we all agree that this is a nice review which requires some minor modifications, as indicated below.

I would like to write some editorial comments;

Please keep authors as indicated in the title page (Hernandez-Alejandro, Ruffolo, Alikhanov, Bjornsson, Torres, Serrablo). Title page and what was entered in the submission system were different.

We are welcome Dr. ********** to be the joint First Author.

However, please omit Dr. ********** since he was not a part of the original invitation and he already has 3 other publications/ contribution in the special issue.

Please keep highlights 125 characters per bullet.

Thank you, we have corrected the manuscript, title, and authors to reflect the directions of the senior editor.

Reviewer #1: The authors present a comprehensive review entitled "ALLPS as a teenager: maturation of technique and best practice for colorectal liver metastases". The manuscript covers important topics including refinement and modifications of indications, technical issues of the procedure, mechanisms of hypertrophy, and special considerations of ALPPS for colorectal liver metastases (CRLM). The paper is accompanied by one illustrative figure and 50 relevant references are quoted. Although the paper is well-written, it needs following modifications:

1. The focus of this review article should be on CRLM. The authors spend a lot of effort in describing the evolution of ALLPS and its application to other indications such as HCC and biliary tumors (page 5) as well as mechanisms of hypertrophy and assessment of hepatic function. Only one paragraph (ALLPS for CRLM) is purely designated to the special aspects of CRLM. If the word count of this section is taken into account, the word count of the CRLM paragraph represents 18-20% of the total manuscript text word count. The authors should explain when liver-first and when primary-first approach needs to considered in ALPPS candidates. Therefore, I recommend removing the content on other tumor entities and other

topics that deviate the content of the paper from the main purpose of the review. The authors should expand the manuscript more towards to all ALPPS aspects in CRLM.

Thank you, we have removed two paragraphs regarding the use of ALPPS for CCA and HCC and expanded the section on CRLM

2. Along with the previous point, I recommend changing the title and keeping the proposed title by the editors "Associating Liver Partition and Portal vein ligation for Stage hepatectomy (ALPPS) procedure for Colorectal Cancer Liver Metastasis".

Thank you, we have changed the title to the requested title.

3. Figure 1 is very informative and presents an excellent summary illustration; however, all recommendations that do not exclusively apply to CRLM should be removed (e.g. HCC, CCA). Please add under the "STOP" category following points: (i) no upfront chemotherapy, (ii) progression under/after neoadjuvant chemotherapy, (iii) unfit for surgery. Please add under the "CAUTION" category: (i) symptomatic primary tumors need to be first addressed (primary-first approach) before ALPPS can be considered for synchronous CRLM.

Thank you for these thoughtful suggestions, the figure has been amended as suggested.

4. The title of figure 1 needs to be "Best-practice recommendations for associating liver partition with portal vein ligation for stage hepatectomy (ALPPS) in patients with colorectal liver metastases".

Thank you, the title has been changed as requested.

5. One of the coauthors of this review is also investigator of the LIGRO trial. A very recently accepted paper of this group shows superior survival outcome of the ALPPS compared to TSH group. These findings were also presented by the LIGRO group at the 3rd ISLS Meeting in Istanbul. The talk entitled "ALPPS improves survival compared with TSH in patients affected of CRLM - survival analysis from the randomized controlled trial LIGRO" was presented by Kristina Hasselgren. Therefore, I would strongly recommend including the most recent findings of this trial in the revised mansucript.

Indeed since the first writing of this manuscript the seminal results on overall survival from the LIGRO trial have been published. The manuscript now reviews extensively the findings from the LIGRO trial and includes a figure from these findings.

6. Although figure 1 is excellent, the review would benefit from additional figures and/or tables. An example could be a table summarizing ALPPS studies in patients with CRLM (please see doi: 10.1002/jso.25435).

Thank you, we have included an additional figure which includes a table as well.

7. Please include reference doi: 10.1016/j.hpb.2018.12.003.

Thank you we have included this reference.

Reviewer #3: I read the manuscript ID IJS-D-19-01002 with great interest. The authors summarized the development of ALPPS with a great descriptive figure.

I think the manuscript will be vey useful after some minor corrections.

1- Since the title says ALPPS in CRLM, more details of the role of ALPPS in CRLM should be included.

Thank you, we have re-focused the manuscript from one on ALPPS more generally to one on ALPPS for CRLM with removal of discussion on its role in other cancers and with an expanded discussion on exciting recently published trial data.

2- A table which summarizes all studies (which are not too many) of ALPPS in CRLM will be very useful for the readers.

Thank you, we have included a table demonstrating the survival following ALPPS for contemporary studies (Table 1).

3- Highlight bullet # 3 and # 4 are same. Please omit one.

Thank you, these bullets have been reconciled

4- There is no need to cite reference in the abstract.

The citation was removed from the abstract, thank you.

5- Last sentenced in the abstract there is a typo "...of CRLM IS codified.'

Thank you, we have addressed this error.

To the Editors,

Thank you for this opportunity to review Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy for Colorectal Liver Metastases. All authors have reviewed the work and agree with the content of the manuscript. Finally, the authors have no relevant conflicts to disclose.

Sincerely,

Roberto Hernandez-Alejandro, MD
Corresponding Author

Credit Author Statement

RH Developed the concepts, organized the effort to prepare the manuscript, and edited the manuscript. LR developed the concepts, wrote the manuscript and developed the figures and tables. RA, BB, OT, and AS Developed the concepts and provided critical edits to the manuscript, and All authors approve of the final version of this manuscript.

Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) Procedure for Colorectal Liver Metastasis

Roberto Hernandez-Alejandro[1,2,] Luis I. Ruffolo,[1,3] Ruslan Alikhanov,[4] Bergthor Björnsson,[5] Orlando Jorge M Torres,[6] Alejandro Serrablo,[7]

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7. Division of Surgery, Miguel Servet University Hospital and University of Zaragoza School of Medicine, Zaragoza, Spain

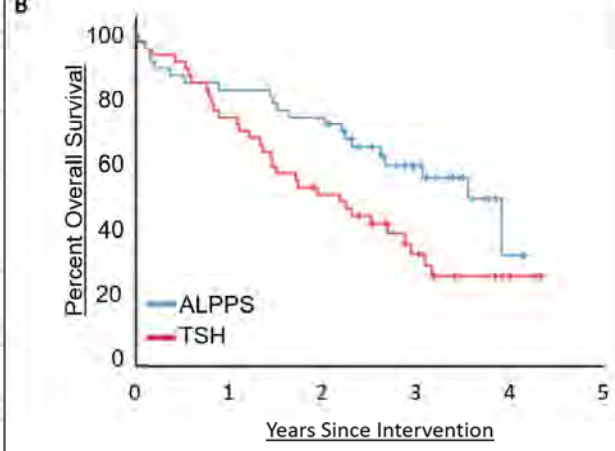
Abstract:

Since first described, Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) has garnered boisterous praise and fervent criticism. Its rapid adoption and employment for a variety of indications resulted in high perioperative morbidity and mortality. However recent risk stratification, refinement of technique to reduce the impact of stage I and progression along the learning curve have resulted in improved outcomes. The first randomized trial comparing ALPPS to two stage hepatectomy (TSH) for colorectal liver metastases (CRLM) was recently published demonstrating comparable perioperative morbidity and mortality with improved resectability following ALPPS. In this review, as ALPPS enters the thirteenth year since conception, the current status of this contentious two stage technique is presented and best practices for deployment in the treatment of CRLM is codified.

A

Perioperative Outcome	ALPPS (n=48)	TSH (n=49)
Resection Rate	98%	57%
R0 Resection	77%	57%
90-day mortality	8%	6%
Liver-first approach	40%	37%
Clavien-Dindo Grade 3a or greater complication	43%	43%
1 year recurrence-free-survival	46%	45%

B



Number at risk

ALPPS	48	40	35	18	2	0
TSH	49	36	24	10	2	0

Figure 1: (A) LIGRO Trial intermediate clinical and surgical outcomes. (B) Overall survival analysis for patients randomized to ALPPS vs. TSH with unresectable colorectal liver metastases and insufficient future liver remnant. Median survival estimate 46% vs. 26% (95% CI 34–59 and 16– 36, respectively; P= 0.028). Reproduced from *Hasselgren et. al. Ann. Surg, 2019 [54,58,59]*. Abbreviations: ALPPS; associating liver partition with portal vein ligation for staged hepatectomy, TSH; two stage hepatectomy

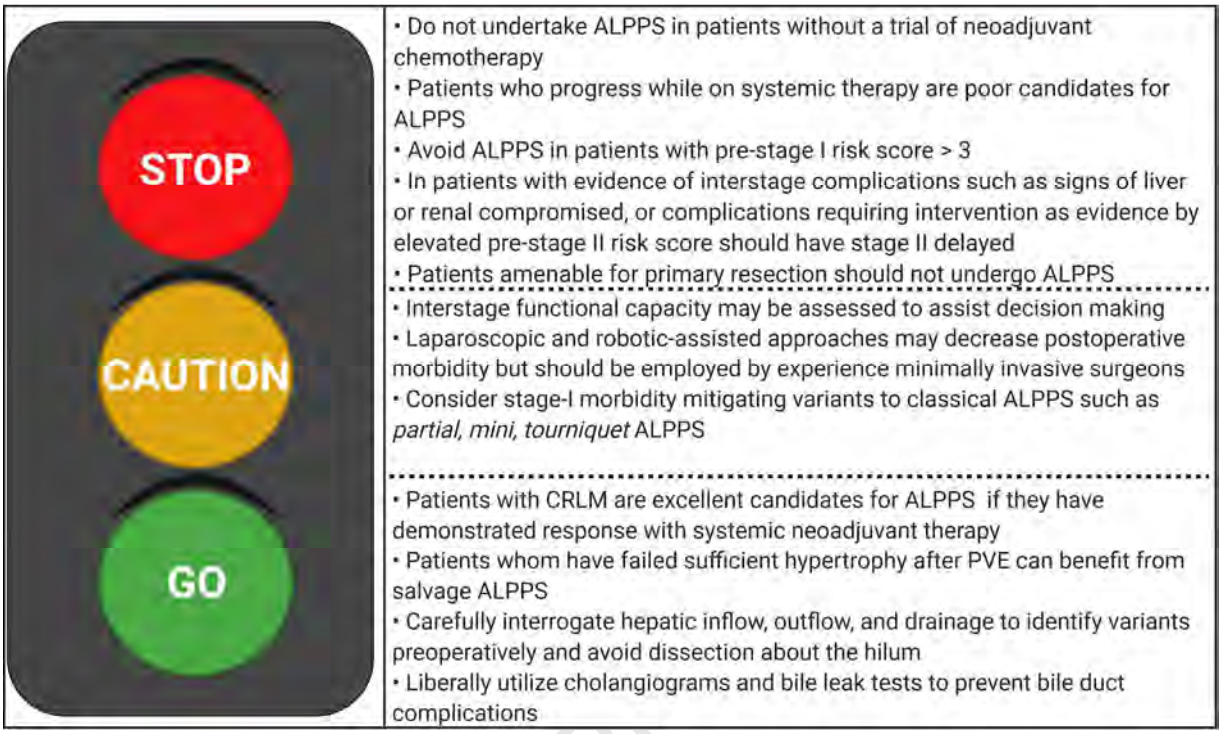


Figure 2: Best-practice recommendations for Associating Liver Partition with Portal Vein Ligation for Stage Hepatectomy for Colorectal Liver Metastases. Abbreviations: ALPPS; associating liver partition with portal vein ligation for staged hepatectomy, CRLM; colorectal liver metastasis

Year	Reference	Design	Patients	1 year Survival	2 year survival	3 year survival	5 year survival
2014	Schadde [9]	Observational	141	76%	63%	-	-
2015	Lang [60]	Observational	7	-	-	64%	
2015	Ratti [53]	Observational	12	92%	-	-	-
2016	Adam [52]	Observational	17	-	42%		
2016	Björnsson [61]	Observational	23	83%	59%	-	-
2017	Olthof [62]	Observational	70	-	62%	-	-
2017	Wanis [50]	Observational	58	93%	66%	50%	-
2018	Serenari [63]	Observational	26	83%	-	49%	-
2019	Linecker [64]	Observational	213	84%	66%	54%	34%
2020	Hasselgren [59]	RCT	48	83%[a]	73%[a]	61%[a]	-

Table 1: Overall Survival after Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy for Colorectal Liver Metastases. (a) Unpublished data from LIGRO trial. Abbreviations: RCT; randomized control trial.

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2017	Wanis [50]	Observational	58	93%	66%	50%	-
2018	Serenari [63]	Observational	26	83%	-	49%	-
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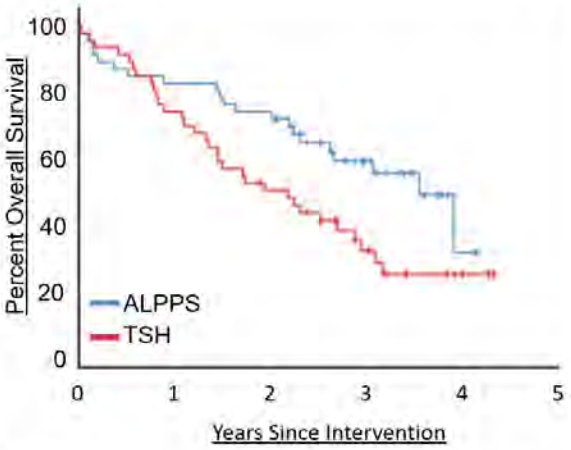
B



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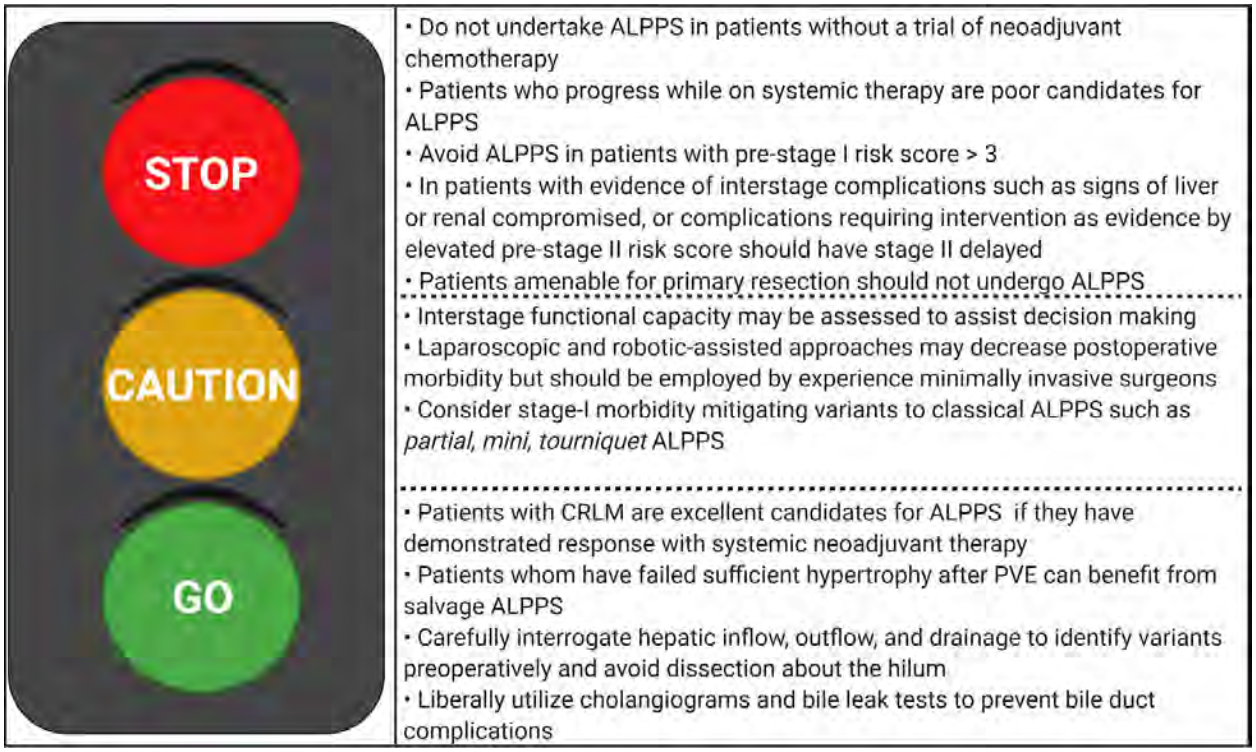

Figure 2: Best-practice recommendations for Associating Liver Partition with Portal Vein Ligation for Stage Hepatectomy for Colorectal Liver Metastases. Abbreviations: ALPPS; associating liver partition with portal vein ligation for staged hepatectomy, CRLM; colorectal liver metastasis

Summary:

- ALPPS has demonstrated excellent ability to achieve resectability compared to portal vein embolization (PVE) and two-staged hepatectomy (TSH) in patients with colorectal liver metastases (CRLM) and insufficient future liver remnant (FLR).
- Outcomes with ALPPS for CRLM have improved and are comparable to other major hepatectomies.
- There is no evidence that the enhanced hypertrophy generated by ALPPS is oncologically inferior to techniques such as PVE or portal vein ligation (PVL).
- ALPPS is a single tool in a broader armamentarium that should not be overused or misused.
- Patient's colorectal cancer (CRC) biology should be considered when considering surgical intervention; poor tumor biology is rarely defeated by herculean surgery.

International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories, then this should be stated.

Please state any conflicts of interest

None

Please state any sources of funding for your research

None

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

Not pertinent

Research Registration Unique Identifying Number (UIN)

Please enter the name of the registry, the hyperlink to the registration and the unique identifying number of the study. You can register your research at http://www.researchregistry.com to obtain your UIN if you have not already registered your study. This is mandatory for human studies only.

1. Name of the registry:

2. Unique Identifying number or registration ID:

3. Hyperlink to the registration (must be publicly accessible):

Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

All authors were involved in the concept. LIR and RH wrote the manuscript, all authors were involved in editing of content.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. Please note that providing a guarantor is compulsory.

Roberto Hernandez-Alejandro, MD

All data were reviewed from cited literature.