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ALPPS: Challenging the concept of unresectability – A systematic review

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ABSTRACT

Introduction: Hepatic resection for malignancy is limited by the amount of liver parenchyma left behind. As a result, two-staged hepatectomy and portal vein occlusion (PVO) have become part of the treatment algorithm. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been recently described as a method to stimulate rapid and profound hypertrophy. **Materials and methods**: A systematic review of the literature pertaining to ALPPS was undertaken. Peer-reviewed articles relating to portal vein ligation (PVL) and *in situ* split (ISS) of the parenchyma were included. **Results**: To date, ALPPS has been employed for a variety of primary and metastatic liver tumors. In early case series, the perioperative morbidity and mortality was unacceptably high. However with careful patient selection and improved technique, many centers have reported a 0% 90-day mortality. The benefits of ALPPS include hypertrophy of 61–93% over a median 9–14 days, 95–100% completion of the second stage, and high likelihood of R0 resection (86–100%). **Discussion**: ALPPS is only indicated when a two-stage hepatectomy is necessary and the future liver remnant (FLR) is deemed inadequate (<30%). Use in patients with poor functional status, or advanced age (>70 years) is cautioned. Discretion should be used when considering this in patients with pathology other than colorectal liver metastases (CRLM), especially hilar tumors requiring biliary reconstruction. Biliary ligation during the first stage and routine lymphadenectomy of the hepatoduodenal ligament should be avoided. **Conclusions**: A consensus on the indications and contraindications for ALPPS and a standardized operative protocol are needed.

1. Introduction

Hepatic resection is the only potentially curative treatment for both primary liver tumors and selected hepatic metastases. However, this is limited by the amount of functional liver parenchyma left behind following resection. Both the volume and the function of the future liver remnant (FLR) determine whether or not hepatic resection is safe. Hepatobiliary surgeons go to great lengths to preserve adequate FLR in an attempt to avoid postoperative liver failure (PLF). When preoperative liver function is normal, an FLR of 30% is generally regarded as sufficient for adequate liver function [1]. In the setting of chemotherapy-related injury or cirrhosis, patients require a FLR of 40% or greater [1–4].

The number of patients who are candidates for hepatic resection has increased due to improved systemic chemotherapies and the development of techniques to increase the FLR by inducing liver hypertrophy. Advances in liver surgery over the last 20 years, in large part, have come as a result of manipulations to redistribute portal venous blood flow to the liver by portal vein occlusion (PVO), resulting in compensatory hypertrophy of the FLR. Two-stage hepatectomies have been described to deal with bilobar liver tumors, and this can be used in conjunction with portal vein ligation (PVL), or percutaneous portal vein embolization (PVE) [5–11]. The most common causes for failure to complete surgical resection after PVO are inadequate hypertrophy of the FLR or interval disease progression. In a meta-analysis by Abulkhir et al., which identified 1088 patients undergoing PVE, 15% failed to undergo definitive resection [12]; other centers describe rates as high as 19–33%

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Table 1
Summary of reported outcomes of ALPPS from all case series >5 cases.

	Study design	Institution	Year of publication	Number of cases	Indication	Volume hypertrophy (%)	Completion stage 2 (%)	R0 resection (%)	Morbidity ≥ IIIb (%)	Bile leak (%)	PLF (%)	90 day Mortality (%)	Median follow-up	Recurrence (%)
Ratti et al.	Observational	Single	2014	6	CC (2) GB (1) CRC (3)	63	100	100	50	33	50/50 0	17	–	–
Schadde et al.	Comparative	Multiple	2014	48	CRC(26) HCC(3) CC(12) Other(7)	77	100	98	42	23	50/50 6	15	1	54
Hernandez et al.	Observational	Single	2014	14	CRC (14)	93	100	86	14	0	50/50 29	0	9 Months	14
Schadde et al.	Observational	Multiple	2014	202	CRC(141) HCC(17) CC (19) NET(8) GB (6) Other(11)	80	98	91	28	17	9	9	9 Months	40?
Sala et al.	Observational	Single	2012	10	CRC(7) CC(1) NCNNELM(1) HCC(1)	82	100	100	0	20	ISGLS 20 Grade A	0	6 Months	20
Alvarez et al.	Observational	Single	2013	15	CRC(10) HCC(1) CC(1) NET(2) Other(2)	78	100	100	27	20	ISGLS 20	0	6 Months	27
Robles et al.	Observational	Single	2014	22	CRLM(17) RCC(2) HCC(1) GIST(1) NE(1)	61	100	100	9	23	ISGLS 14	9	6 Months	5
Nadalin et al.	Observational	Single	2014	15	CRC(5) CC(9) HCC(1)	87	100	87	–	13	–	29	17 Months	29
Torres et al.	Observational	Single	2013	39	CRC(32) CC(3) Sar(2) HCC(1) Benign(1)	74	95	100	–	10	3	13	–	–
Li et al.	Observational	Single	2013	9	CRC(3) CC(6)	87	100	100	33	22	ISGLS 22	22	–	–
Schnitzbauer et al.	Observational	Multiple	2012	25	CRC(14) HCC(3) CC(4) GB(1) Other(3)	74	100	96	44[b]	24	–	12	6 Months	20
Knoefel et al.	Comparative	Single	2013	7	–	63	100	–	57[b]	29	0	14[a]	–	–
Oldhafer et al.	Observation	Single	2014	7	CRC	76	100	100	0	0	–	0	15 Months	87

[a] 30-Day morbidity.
[b] Morbidity reported at ≥IIIa.

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[13–15]. The most common reason for non-resection was progression of disease (10%) followed by inadequate hypertrophy of the remnant liver (2%) [12].

An innovative, accelerated two-staged technique utilizing PVL and *in situ* split (ISS) of hepatic parenchyma was first described in 2012 [16]. This technique, named Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS), has been demonstrated to induce rapid and extensive hypertrophy and has challenged the concept of unresectability [16,17]. However, much controversy has surrounded this procedure, and both safety and long-term oncologic outcomes have been questioned [18,19].

2. Materials and methods

2.1. Search strategy

Both PubMed and Medline were searched using the following combinations of key terms: associating liver partition and portal vein ligation, ALPPS, portal vein ligation, and in-situ split. Articles were identified by searching the databases from their inception to November 24, 2014. A secondary search of the reference lists of these articles was performed and articles meeting pre-specified criteria were included (Table 1)

2.2. Inclusion and exclusion criteria

All articles reporting on the novel technique of portal vein ligation and *in situ* splitting of liver parenchyma for the purpose hepatic resection for malignancy were considered for inclusion into this systematic review. Only articles published in the English language peer-reviewed literature were included. Letters to the Editor were included if they were judged by the authors to contain novel information or original opinions. Articles were excluded if they were found to be reporting on a redundant patient population from another article by the same author. In this case, only the more comprehensive article containing the larger patient cohort was included.

2.3. Data extraction

Six reviewers (KB, JH, KL, SB, KP, RHA) independently reviewed each publication to determine if they met the pre-specified inclusion criteria. Group consensus was obtained for inclusion or exclusion of each article. All reasons for exclusion are documented in Fig. 1.

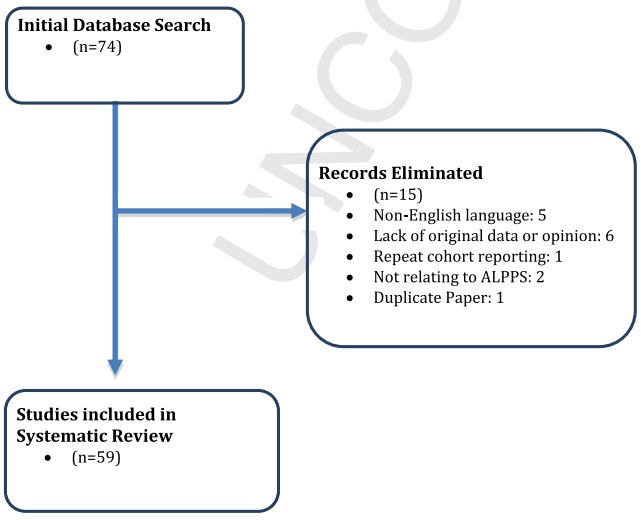

Fig. 1. Flowchart of study selection.

3. History of ALPPS

3.1. Creation by chance

First performed in 2007, ALPPS owes its creation at least in part to chance. Dr. Hans Schlitt from Regensburg, Germany had planned to carry out an extended right hepatectomy for a perihilar cholangiocarcinoma, but intraoperatively was faced with an insufficient FLR. He performed a left hepatico-jejunostomy, and divided the liver parenchyma along the falciform ligament in order to achieve optimal positioning of the hepatico-jejunostomy. The right portal vein was ligated in an attempt to induce hypertrophy of the contralateral side [20]. On postoperative day 8, a computed tomography (CT) scan revealed that the left lateral segment of the liver had extensive hypertrophy and the decision was made to resect the right liver [20].

3.2. International uptake

The procedure was first formally described in a series of three patients in 2011 as a poster at the European-African Hepato-Pancreato-Biliary Association conference by a group from Mainz, Germany [20]. Following this initial poster presentation, the yet unnamed procedure was taken up by an Argentinian group [21]. They reported its application to three cases that were previously considered unresectable owing to inadequate FLR volume [22]. In 2012, Schnitzbauer et al. published their landmark cases series of 25 patients [16]. An editorial in 2012 by de Santibanes and Clavien proposed a name – Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) [20]. ALPPS has since been adopted and adapted by many centers around the world, and has elicited much discussion and debate in the global hepatobiliary community.

In 2012, an international ALPPS registry was created. Currently there are more than 430 ALPPS procedures registered from 75 centers across the world. (www.alpps.net/q=registry).

4. Pathophysiology of liver regeneration

Factors affecting regeneration have been summarized by the "humoral" and "blood flow" theories. The liver generates cytokines, growth factors and hormones, which play an integral role in initiation, propagation and termination of liver regeneration [23–25]. Proliferation of hepatocytes is known to be mediated by hemodynamic changes [26–28] and is particularly sensitive to alterations in portal flow [29]. Knowledge of the effect of these changes in portal flow to the liver became the impetus for the majority of surgical advancements in liver resection.

4.1. Reasons for rapid hypertrophy

The increase in portal flow to the FLR after PVO is an important trigger for liver regeneration and is the most amenable to surgical manipulation. Wilms et al. identified portal neo-collaterals to segments of the liver with occluded portal flow by performing *ex-situ* angiography after PVE and PVL [30]. This recanalization of branches of the embolized portal vein has been suggested as one of the reasons for failure of adequate hypertrophy after technically successful PVE [26,31,32]. The addition of ISS to PVL prevents the formation of vascular collaterals, which may explain the greater hypertrophy seen in ALPPS [31,32]. Manipulation of the liver intraoperatively in the first stage of ALPPS also creates a traumatic

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stimulus, which may also contribute to the hypertrophy [32].

However, the proliferative stimulus following PVO affects not only hepatocytes, but also tumor cells in the affected hemiliver. Kokudo et al. described increased proliferative activity (tumor Ki-67 labeling index) of intrahepatic metastases in the embolized liver after PVE [33]. This same effect on the tumor cells is also noted with ALPPS despite a shorter interval between PVO and liver resection. Kobayashi et al. reported tumor biopsy results of the same liver lesion at both the first and second stage laparotomy for ALPPS. In this small series they found an increase in Ki-67 labeling index from 60% at the first stage to 80% at the second stage [34].

4.2. Reasons for failure of hypertrophy

It has been suggested that the complete redirection of portal flow to one hemiliver can lead to portal hypertension, similar to the portal hypertension seen in "small for size" syndrome [35–37]. The term "small-for-size" syndrome was first used in liver transplantation, although the mechanism is similar to that in PLF – insufficient liver mass for the resultant blood flow [35,38].

Further delineation of risk factors has been difficult due to the small sample size of published series. The effects of preoperative chemotherapy on the liver have been postulated to increase the risk of inadequate hypertrophy of the FLR. The majority of candidates for ALPPS have undergone prolonged preoperative chemotherapy ($\geq$9 cycles) [37]. The magnitude of effect of chemotherapy on liver regeneration is debated, with many contradictory studies [39–42].

4.3. Assessment of liver regeneration

Volumetric analysis is operator-dependent and only gives information about size. Discrepancies exist between volumetric assessment, laboratory tests, and functional evaluations of the remnant liver postoperatively. Nadalin et al. found a 40% decrease in galactose elimination capacity (GEC) in living liver transplant donors that lasted as long as three months after surgery, despite normalization of liver biochemistry [43]. Most tests imply total liver functionality without taking into account the regional function of the FLR. Scintigraphic imaging before and after the first stage of ALPPS may assist in the measurement of FLR function and the ideal timing for resection, as scintigraphic isolation of the FLR is easier after ISS [44]. Ardilles et al. also report the use of scintigraphy to confirm a sufficient FLR prior to moving forward with completion surgery [22]. However, the level of evidence is limited, and further study is required. Intraoperative assessment may be possible with the use of indocyanine green (ICG) [45–48]. Muralidheran et al. proposed intraoperative ICG clearance assessment of the actual FLR function before the first stage of ALPPS [49].

5. Technical considerations

It has been suggested that the discrepancy of the reported results may be due to a combination of the surgical learning curve, ill-defined indications, and a wide variation of malignancies that necessitate resection. Kokudo et al. emphasized the necessity to standardize the technical aspects of the technique and to improve the safety of this procedure [50].

5.1. Initial technical description

After exploratory laparotomy, the liver is completely mobilized from its attachments. Segments 2 and 3 are cleared of tumor with wedge resections as required. The structures within the porta hepatis are then skeletonized. Subsequently the right portal vein is ligated and divided while preserving the right hepatic duct and right hepatic artery. Following this, a total or near total parenchymal partition is performed at the level of the falciform. After parenchymal transection, a plastic bag is used to cover the deportalized liver to avoid adhesions prior to the second stage and to collect the bile in the case of a bile leak [16].

After a mean interval of 9 days, CT volumetry is utilized to confirm hypertrophy of the FLR. Repeat laparotomy is performed and the plastic bag is removed. The right hepatic artery is ligated and divided along with the right bile duct. The right and middle hepatic vein, which provide venous drainage, into the vena cava, are ligated and divided. When necessary, the biliary system is reconstructed with a Roux-en-Y hepaticojejunostomy. The FLR is fixed to the anterior abdominal wall to prevent rotation. Drains are placed in the surgical bed.

5.2. Modifications to the initial description

5.2.1. Non-touch technique

The classic approach describes full mobilization of the liver, and complete dissection and exposure of the retro-hepatic inferior vena cava (IVC) [16]. A group from Hamburg, Germany published the use of a non-touch technique which they termed the "hybrid ALPPS", and it has since been adopted by other centers [51,52]. The idea is to avoid manipulation of the right side of the liver to hypothetically improve oncological outcomes [53,54]. Using this technique the partition is completed using an anterior approach without mobilization of the right hemiliver and the hepatoduodenal ligament is left intact. Right PVE is performed by interventional radiology in the first few days following the operation. It is reported that there is less inflammation surrounding the liver at the second stage. Although there is a hypothetical concern that aggressive tissue handling of the tumor may induce hematologic spread of malignancy, currently there is no published data supporting a superior oncological outcome with this alternative approach. Other authors caution against the anterior approach because of the inability to achieve optimal vascular control during such a technically complex procedure [55].

5.2.2. Bile duct ligation

There have been publications advocating for right bile duct ligation to further enhance the FLR hypertrophy. Biliary obstruction is believed to induce atrophy of the obstructed liver triggering a compensatory hypertrophy of the FLR. However, this has been associated with a higher rate of bile leak and biloma formation, as well as increased difficulty of the second stage due to dense adhesions at the porta hepatis [54]. As such, routine bile duct ligation should not be performed.

5.2.3. Approach to the hepatoduodenal ligament

The early publications describe hepatoduodenal ligament dissection to allow for clear identification and eventual ligation of the portal structures, as well as a routine lymphadenectomy [16,21,56]. However, other authors have cautioned that extensive dissection of the hepatoduodenal ligament increases the likelihood of segment 4 ischemia and potentially increases the risk bile leak and resulting septic complications [57]. Segment 4 ischemia has been widely recognized as a potential source of morbidity in the setting of ALPPS and some surgeons even advocate for routine resection of segment 4 [58].

5.2.4. Preservation of the middle hepatic vein

In the early descriptions of ALPPS, the middle hepatic vein was ligated during the first stage [16]. However, our group routinely preserves this vein to ensure proper outflow, avoiding congestion of segments 4, 5 and 8, and this is believed this to be a critical

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maneuver to decrease the risk of ischemia, hepatic necrosis and subsequent bile leak [57].

5.2.5. Liver tourniquet

In 2013, Pena Moral et al. described another modification, the use of a liver tourniquet in place of ISS, termed ALTPS (Associating Liver Tourniquet and Portal Ligation for Staged Hepatectomy) [59]. The proposed benefit is decreased technical complexity and shorter operating times for the first stage of surgery, therefore potentially decreasing morbidity. Instead of in-situ split, a thick vicryl suture is positioned around the liver following either Cantlie's line or to the right of the umbilical fissure through a 1 cm deep groove in the parenchyma. The tourniquet is then tied tightly enough to occlude all collateral vessels between lobes. This is confirmed with intra-operative ultrasound (IOUS). The authors reported hypertrophy of the FLR of 150% in this case report [59].

5.2.6. Radio-frequency assisted liver partition (RALPP)

Another new technique to avoid the complications of liver partition was recently presented by a group from the United Kingdom. After right PVL, an in-line radiofrequency ablation (RFA) probe was applied to the parenchyma at the site of demarcation. They showed hypertrophy of the FLR of 62.3% over a mean interval of 21.8 days [32].

5.2.7. Minimally invasive approach

There have been reports of laparoscopic ALPSS with the proposed benefit of minimizing adhesions [60]. In the early laparoscopic reports, the second stage is completed using an open technique. More recently, totally laparoscopic ALPPS has been described [61–63].

5.2.8. Segmental modifications

Various modifications of ALPPS that alter the specific segments comprising the FLR have been described including left-sided ALPPS, segment 4 ALPPS and monosegmental ALPPS [64–66].

Segment 4 ALPPS, in which the FLR is segment 4, has been described by multiple authors, including our own group [64,65]. This challenging modification consists of a left lateral sectionectomy, metastesectomy of segment 4, right PVL, and *in situ* split along Cantlie's line during the first stage of the operation. Before parenchymal transection, the vascular inflow and outflow of segment 1 and 4 is assessed with IOUS after clamping the right portal vein.

6. Outcomes

The published outcomes of the ALPPS procedure come from observational studies, many of which are small case series. The majority of these publications are single-institutional studies, while a few are multi-institutional. The most commonly reported primary outcomes are the percentage hypertrophy of the FLR, the ability to obtain a microscopically negative (R0) resection, and percentage of patients who complete both stages of the operation. Post-operative mortality and morbidity have been studied as secondary outcomes, while oncologic outcomes have been sporadically reported.

6.1. Demographics

The patients selected for the ALPPS procedures are generally younger, in their sixth and seventh decades of life, with mean or median age ranging from 54 to 67 years [67,68]. The procedure has been described most commonly for CRLM, with the remaining indications comprised of cholangiocarcinoma, gallbladder cancer, hepatocellular carcinoma, neuroendocrine tumors and other liver metastases. Of the studies reporting on CRLM, administration of preoperative chemotherapy was common, and studies reported this in 79–100% of patients [16,68]. Furthermore, the reported studies are consistent in utilizing ALPPS only for patients whom the FLR is deemed insufficient. As such, the median preoperative standardized future liver remnant (sFLR) ratio ranges between 0.19 and 0.27 [17,57,68,69].

6.2. Primary outcomes

Following a median interval of 9–14 days, studies have consistently reported an impressive hypertrophy of 61–93% increase in volume [16,17,56,57,68–76]. Ninety-five to 100% of patients undergoing the first stage of ALPPS completed the second stage, and 86–100% had a R0 resection [16,17,56,57,68–76].

6.3. Morbidity and mortality

The main criticisms of ALPPS are centered on the high morbidity and morality rates associated with the procedure. There is inconsistency in the reporting of significant morbidity, although most papers define this as Clavien–Dindo classification ≥grade IIIB [56,57,68]. The largest study of 202 patients cites a major morbidity of 28% [69]. Ninety-day mortality rates have been more variable, namely due to the small sample sizes of many of the series reported. The sentinel German study by Schnitzbauer et al. reported a 12% 90-day mortality, which raised critical discussion amongst the international community [16]. Other small series reported rates that are even higher, ranging from 22% to 29% [63,71], although these are small series and caution must be taken in interpreting these results. Furthermore, multiple centers have now reported series with no 90-day mortalities occurring [56,57,70,76]. Biliary reconstruction, which is commonplace when ALPPS is performed for hilar cholangiocarcinoma or gallbladder cancer, is consistently seen to have greater morbidity and mortality [16,68,71]. Our group recently published a series demonstrating low morbidity (14% Clavien–Dindo ≥ IIIB) and no mortalities when ALPPS is reserved only for patients with CRLM [57]. Recently, Schadde et al. described resection for non-colorectal liver metastases as an independent predictor for severe complications [69].

6.4. Comparison with conventional two-stage hepatectomies

There have been few studies directly comparing ALPPS to conventional two-stage hepatectomies, although ALPPS is not intended to supplant conventional two-stage hepatectomies, but rather to expand the armamentarium for hepatic resection. Shindoh et al. published a retrospective review of 144 patients undergoing portal vein embolization and performed a comparative analysis to the 25 patients undergoing ALPPS from the original German paper [18]. They showed that there were similar hypertrophy rates with 74% in the ALPPS group and 62% in the PVE group. Overall, major morbidity (Clavien–Dindo ≥ IIIA) was not significantly different between the 2 groups (40% ALPPS versus 33% PVE), however bile leaks (24% versus 5.8%), sepsis (20% versus 0%), and re-laparotomy (28% versus 2.9%) were significantly higher in the ALPPS group. Liver-related mortality was higher in the ALPPS group (12% versus 5.8%), but this did not reach statistical significance [18]. Furthermore, 27.8% of the patients undergoing PVE did not reach the second stage due to short interval disease progression or insufficient liver regeneration.

Schadde et al. published a retrospective multicenter study comparing PVO to ALPPS using data obtained from four major centers [17]. While they did recognize the trend toward higher morbidity and mortality associated with ALPPS when compared to

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PVO (15% versus 6% 90-day mortality and 13% versus 9% PLF after the second stage), more patients in the ALPPS group achieved completion resection (83% versus 66%) and recurrence at 12 months was comparable (54% versus 52%). In contrast to Aloia et al., there was only a 34% increase in FLR in the PVO group compared to 77% in the ALPPS group, showing benefit from ALPPS in this regard.

6.5. Long-term follow-up

As the time from the original publication increases, long-term data is becoming available. Disease-free survival (DFS) at a median of 180 days ranges from 73% to 95 %, and this decreases to between 46 and 60% at 1 year [17,57,67,69]. The 1 and 2-year DFS for patients undergoing ALPPS for CRLM from the ALPPS registry is 59% and 41% respectively [69]. One small study has reported an alarmingly high liver-specific recurrence rate of 86% at 15 months [76]. Overall survival (OS), however, is encouraging at 86–100% at 6 months, dropping to 59% at 2 years [16,57,67,69].

7. Controversies

7.1. Time to reoperation

Proponents of ALPPS have long implied that the short interval to re-operation and earlier removal of tumor burden improves oncologic outcomes [20,67]. The primary rationale is that fewer patients fail to complete the second stage. The percentage of ALPPS patients completing their second stage resection is nearly 100%, and this is certainly not the case with conventional two-staged hepatectomies, which have a 28–34% failure of completion of the second stage [17,18]. However, critics of ALPPS argue that patients who progress after the first stage do not have favorable tumor biology, and are likely to have early recurrence following ALPPS [18,77]. The longer length of time allows surgeons to select out those who would likely not benefit from resection and save them the risks of a major surgery. Other groups use response to pre-hepatectomy systemic chemotherapy as a marker for favorable tumor biology [57,78]. Schadde et al. published comparable tumor recurrence rates at 12 months between ALPPS and PVO (54% versus 52%) [17]. This suggests that the more aggressive early resection approach may not result in earlier tumor recurrence. Furthermore, some have hypothesized that a shorter time off of chemotherapy will lead to better oncologic results [20,56] although this remains to be demonstrated statistically.

7.2. Salvage ALPPS procedure

Several groups have opined that not only is ALPPS an alternative to conventional two-staged hepatectomies, it is also an effective salvage therapy for failed PVE or PVL [79]. Clavien et al. published a case series of three patients showing successful resection following failed portal vein occlusion [80]. However, two of the three patients had recurrence of disease, albeit extrahepatic recurrence, at one year.

7.3. Long-term oncologic outcomes

ALPPS is still a relatively novel technique in the infancy of its development. While it has promising potential in managing previously unresectable liver malignancies, allowing surgeons to continue to push the boundaries of resectability, there is insufficient data to suggest that the radical nature of the procedure translates into long-term disease-free and overall survival. Early data suggests that recurrence, both liver-specific and extrahepatic, is substantial [17,76]. In the largest series of patients from the ALPPS registry, the 2-year DFS is 41% for CRLM [69]. In an MD Anderson series, the 2-year DFS is 25% following PVE and two-stage hepatectomy [81], suggesting that ALPPS at least provides comparable oncologic outcomes in this group.

8. Discussion

Thus far, outcomes in ALPPS in the setting of CRLM seem to be superior [57,69] and therefore the strongest indication for ALPPS is in the setting of CRLM. Pre-operative chemotherapy can be considered prior to ALPPS and the response evaluated as a surrogate for tumor biology. Due to the increased incidence of bile leaks and major septic complications, ALPPS should be reserved only for patients that require a two-stage hepatectomy with an expected FLR of less than 30%. Multiple studies have shown increased morbidity and mortality following biliary reconstruction with ALPPS [16,68,71]. At this time we would caution against the use of ALPPS for hilar tumors requiring biliary reconstruction. Given the demanding physiologic stress associated with two short interval laparotomies, relative contraindications to ALPPS should include poor pre-operative performance status, and age over 70 years.

Many technical variations of ALPPS have been described. A large proportion of the morbidity of this procedure is attributed to biliary leak and the resulting septic complications. For this reason ligation of the bile duct during the first stage in an attempt to induce hypertrophy of the FLR should be strongly avoided. Furthermore, skeletonizing the hepatoduodenal ligament to facilitate a routine lymphadenectomy has the potential to devascularize the bile duct, and should be circumvented as well.

9. Conclusions

ALPPS is a novel surgical technique for resection of hepatic malignancies that has fostered both excitement and debate within the international hepatobiliary community. This technique offers patients with insufficient FLR, many who are considered unresectable by other methods, a chance for cure. High perioperative morbidity and mortality, as well as significant variation in patient selection emphasize the importance of developing clear indications for ALPPS. Furthermore, there is very little consensus on the technical aspects of the procedure, which hampers the ability to reproduce robust results amongst centers. There is a need for a standardized technical protocol for this technically demanding operation, and surgeons performing ALPPS should be adequately trained before offering it to their patients. Early data on long-term oncologic outcomes are promising and comparable to conventional two-stage hepatectomy, but ongoing study is needed.

Ethical approval

None required.

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Author contribution

Bertens, Kimberly: Study design, data collection (systematic review of the literature), writing, editing.

Hawel, Jeffery: Study design, data collection (systematic review of the literature), writing, editing.

Lung, Kalvin: Study design, writing, editing.

Buac, Suzana: Study design, writing, editing.

Pineda, Karen: Writing, editing.

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Hernandez- Alejandro: Study design, writing, editing.

Conflicts of interest

None.

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Q5 [82–95].

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