Variations and adaptations of associated liver partition and portal vein ligation for staged hepatectomy (ALPPS): Many routes to the summit

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Background. *Our aim was to review variations from the originally described associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure and relevant clinical outcomes.*
Methods. *A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (ie, PRISMA) guidelines. A search of PubMed and Google Scholar was conducted until March 2015. Inclusion criteria were any publications reporting technical variations and descriptions of ALPPS. Exclusion criteria were insufficient technical description, data repeated elsewhere, or data that could not be accessed in English.*
Results. *Initial search results returned 790 results; 46 studies were included in the final qualitative analysis. There were several alternatives described to the first stage of complete parenchymal split. Variations included partial ALPPS (partial split; hypertrophy of future liver remnant [FLR] 80–90%), radiofrequency-assisted liver partition and portal vein ligation (mean FLR hypertrophy 62%), laparoscopic microwave ablation and portal vein ligation (FLR hypertrophy 78–90%), associating liver tourniquet and portal ligation for staged hepatectomy (median FLR hypertrophy 61%), and sequential associating liver tourniquet and portal ligation for staged hepatectomy (FLR hypertrophy 77%) with a potential decrease in morbidity particularly after stage I. We analyzed several other variations, including considerations for segment IV, operative maneuvers, use of laparoscopy, identification of biliary complications, and liver containment.*
Conclusion. *The current literature demonstrates a large variability in techniques of ALPPS that limits meaningful statistical comparisons of outcomes. Not physically splitting the liver at the first stage may decrease morbidity; however, randomized controlled trials are needed to determine benefits in technical variations. (Surgery 2016;159:1058-72.)*

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THE TRADITIONAL 2-STAGE HEPATECTOMY for the treatment of liver tumors has been replaced in some situations by the introduction of the technique of associated liver partition and portal vein ligation for staged hepatectomy (ALPPS).[1] ALPPS aims to increase the proportion of patients deemed operable and decrease the dropout rate from the classic, 2-stage liver resection. ALPPS is performed by separating the future liver remnant (FLR) and diseased hemiliver in the first stage with an in-situ "split," in combination with portal vein ligation (PVL). The landmark paper by Schnitzbauer et al[2] showed that rapid hypertrophy of the FLR could be achieved in a very short period of time (median FLR hypertrophy of 74% in 9 days); de Santibanes et al[3] subsequently coined the term ALPPS.

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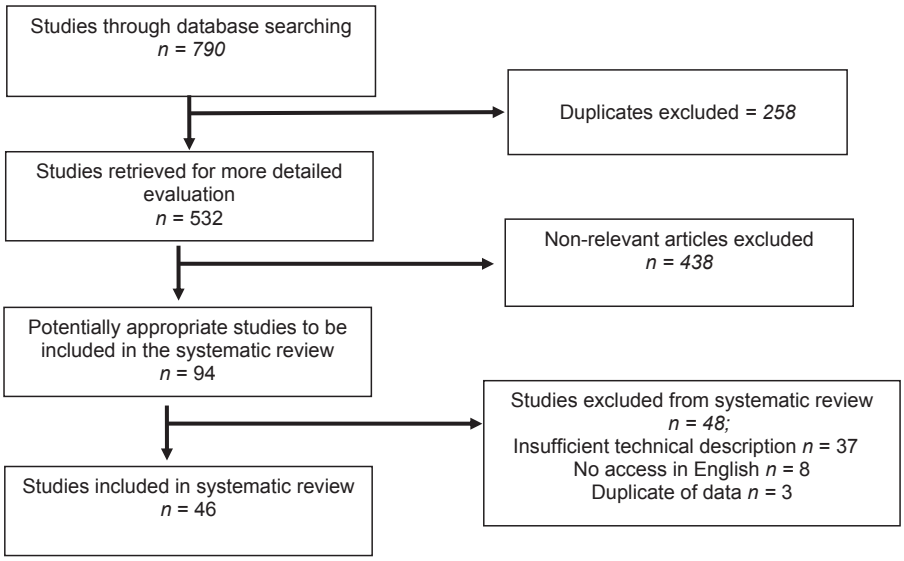

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (i.e., PRISMA) diagram.

The initial report of a serious complication rate (Clavien-Dindo [CD] ≥III) of 44% and a mortality rate of 12% for ALPPS[2] lead to concerns among the surgery community and raised questions regarding its role and indications.[4-6] Recently published data from the ALPPS registry[1] suggested that the high morbidity associated with ALPPS is less when treating patients younger than 60 years of age and those with colorectal liver metastases, whereas those patients with gallbladder cancer and cholangiocarcinoma had poorer outcomes. These studies raise important questions for future patient selection. The results of this more-recent registry report were more encouraging, with a 90-day mortality of 9% and serious complications (≥CD IIIb) of 27%.[1]

The mechanism behind the increased FLR hypertrophy in ALPPS is yet to be determined fully. Traditionally, this hypertrophy was believed related to the cessation of blood flow between the diseased segment/s and the FLR. Schlegel et al[7] describe an rodent study in which they reported increased levels of interleukin-6 in the plasma and increased levels of interleukin-6 and tumor necrosis factor-α in liver tissue 1 hour after step I of ALPPS compared with PVL in both mice and humans. The authors reported that the rapid hypertrophy of the liver parenchyma after step I of ALPPS may be associated with a systemic increase of circulating growth factors released as part of an inflammatory reaction to the parenchymal split.

Since its introduction, ALPPS now acts as an umbrella term under which many variations and adaptations exist. A main driver for further innovation is the goal of decreasing morbidity and mortality while maintaining a more rapid and robust FLR hypertrophy. Within this context, it is vital that each variation should be subject to the same scrutiny and debate to avoid unnecessary harm during the "innovation" phase of development.[8] The aim of this systematic review was to review the literature for variations from the originally described ALPPS technique and summarize relevant adaptations in technique and associated clinical outcomes.

METHODS

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (ie, PRISMA) guidelines. A search of PubMed and Google Scholar was conducted until March 2015. The following search terms were used: ALPPS *or* liver partition *or* portal vein ligation. After deduplication, results were first searched for relevant titles and abstracts. In addition, reference lists were hand-searched for other relevant articles that may have been missed. Inclusion criteria included publications, abstracts, and journal letters describing the ALPPS technique or its technical variations. Exclusion criteria included any publication that could not be accessed in English, did not contain sufficient technical description, or contained data repeated elsewhere. Full-text versions of candidate studies were then retrieved and considered for final inclusion according to agreed-on selection

Table I. Method and outcomes of studies reporting a variation to complete in-situ split in the first stage, with registry data included for comparison

Reference	*Method*	n	*FLR growth (%)*	*Resection type*	*Time between stage 1 + pre-stage 2 imaging, d*	*Time between stage 1 and stage 2, d*
Schadde et al,[1] 2014 *Ann Surg* (Registry)	Complete split	202	Median 80	RH RT ± Sg 1 Other	Median 7	—
Alvarez et al,[9] 2015 *Ann Surg*	Partial split	21	Mean 90	RH RT LT	Median 6	—
Petrowsky et al,[10] 2015 *Ann Surg*	Partial split	6	Median 60	RH RT LT	Median 7	Median 11
Gringeri et al,[16] 2015 *Ann Surg*	Microwave ablation	1	78	RT - Sg 1	—	10
Cillo et al,[17] 2015 *Ann Surg Oncol*	Microwave ablation	1	90	RT	9	15
Sodergren et al,[13] 2015 *HPB*	Radiofrequency ablation	12	Mean 62	RH	Mean 21	—
Robles Campos et al,[18] 2014 *Cir Esp*	Tourniquet (+PVE)	1	77	RT	7 (after PVE)	12
Robles et al,[19] 2014 *Br J Surg*	Tourniquet (+PVL)	22	Median 61	RH RT	7	Median 11

CCI, Comprehensive complication index; *CD*, Clavien-Dindo; *FLR*, future liver remnant; *LT*, left trisectionectomy; *PHLF*, posthepatectomy liver failure; *PVE*, portal vein embolization; *PVL*, portal vein ligation; *RH*, right hepatectomy; *RT*, right trisectionectomy; *Sg*, segment.

criteria. Both literature search and data extraction were undertaken by 2 independent reviewers (M.E. and M.S.), with any disagreement resolved by consensus.

After evaluation of the operative techniques reported in the literature, the following variations were selected for detailed analysis: (1) variations in first-stage splitting of the liver parenchyma; (2) use of ALPPS for salvage or rescue; (3) specific considerations for preventing ischemia of segment IV; (4) specific operative maneuvers (Pringle, hanging, anterior approach); (5) use of a laparoscopic approach at either stage; (6) methods to identify biliary complications; (7) use of a bag or protective film to contain the diseased hemiliver; and (8) number and position of segments resected.

RESULTS

Initial results of the literature search included 790 publications, which was decreased to 532 after we removed duplicates; 94 full-text articles were retrieved for analysis, of which 46 were included in the final qualitative synthesis and assessed for the 8 types of technical variation (Fig 1).

Variations in first-stage splitting of the liver parenchyma. *Partial split.* Two groups compared ALPPS with a technical variation with a partial rather than complete physical separation of the liver parenchyma. Alvarez et al[9] defined a partial split based on the anatomy of the middle hepatic vein. The authors reported that in comparison with a partial split, total parenchymal transection was an independent predictor of postoperative complications (rate of postoperative complications 38% vs 89%, $P = .049$). There was no significant difference in FLR hypertrophy between the partial and total ALPPS group. Petrowsky et al[10] described a partial split that is between 50 and 80% of the total transection surface, with the variation determined by the location and preservation of hepatic veins. The authors reported no difference in liver hypertrophy between partial and full parenchymal splitting (60% vs 61% median FLR hypertrophy), but a much greater morbidity after the first stage was reported when a full parenchymal split was used (rate of severe complications CD ≥ IIIb 0% vs 33%). Both groups discuss the role of increased portal vein pressure and venous congestion within the FLR and hypothesized that

Table I. *(Continued)*

Stage 1				Stage 2					
	Morbidity (%)		PHLF/ biliary leak, %		Morbidity (%)		PHLF/ biliary leak, %	Overall morbidity, %	In hospital mortality, %
Operative time, min	CD < IIIb	CD ≥ IIIb		Operative time, min	CD < IIIb	CD ≥ IIIb			
327	—	—	—	156	—	—	—	40 (≥CD IIIa) 28 (≥CD IIIb)	9.4
—	—	—	—	—	—	—	—	38	—
—	—	0	—	—	—	33	—	15 (median CCI)	0.0
120	—	—	—	215	100	0	0	100	0.0
170	—	—	—	630	0	0	0	—	0.0
—	8	0	—	—	0	17 (>CD III)	—	17	8.3
120	—	—	—	300	100	0	100	100	0.0
125	27	0	22	150	27	9	31	63	9.0

these changes in portal venous flow and pressure propagate postoperative liver injury and failure. Alvarez et al[9] measured portal pressure in both stages for 3 patients and found that clamping of the hepatic artery led to an increase in portal pressure during the first but not the second stage, which was attributed to the arterialized diseased hemiliver playing a role in decreasing the portal pressure until the FLR had increased in size.

Radiofrequency-assisted liver partition with portal vein ligation (RALPP). Radiofrequency ablation (RFA) is an established technique for the treatment of hepatic tumors that uses rapidly alternating currents to produce coagulative necrosis of the hepatic parenchyma.[11] Gall et al[12] reported a modification of ALPPS by using RFA during a laparoscopic first stage to produce a line of avascular necrosis along the future line of transection, termed RALPP. Hypothetically, this technique ceases blood flow from the FLR to the diseased hemiliver while inducing FLR hypertrophy without a physical parenchymal split. In a case-controlled study comparing RALPP with portal vein embolization (PVE) in 20 patients (12 RALPP vs 8 PVE), Sodergren et al[13] reported no bile leaks in the RALPP group after stage I and a comparable liver function profile to PVE after stage II; the mean percentage increase in the FLR volume was 62 ± 16 measured after a mean of 21 ± 7 days after the first stage of RALPP compared with a mean percentage increase of 16 ± 12 after PVE was measured after 52 ± 15 days ($P < .001$). Furthermore, Sodergren et al[14] performed a case-matched comparison of RALPP and ALPPS in 36 patients (12 RALPP vs 24 ALPPS patients matched 1:2) and reported no statistical differences in a median 54% increase (range, 27–95%) in FLR in the RALPP group after a median of 20 days (range, 11–34) compared with a median increase in FLR of 67% (range, 22–182%) after a median of 21 days (range, 13–101) in the ALPPS group. After the first stage, again there were no differences in serious complications, one serious complication (CD ≥ IIIb) in the ALPPS group and none in the RALPP group, and after the second stage, there were 3 serious complications in the ALPPS group and 1 in the RALPP group.

Laparoscopic microwave ablation and portal vein ligation for staged hepatectomy (LAPS). Similar to RFA, microwave ablation (MWA) is used in the treatment of hepatic tumors by the use of electromagnetic microwaves to produce coagulative

necrosis.[15] Gringeri et al[16] reported a case study in which they used MWA during the first stage via a laparoscopic approach along the future plane of transection, with the aim of preventing blood flow to the diseased hemiliver from the FLR and inducing FLR hypertrophy, termed LAPS. The authors reported a 78% FLR growth and one CD II complication, with minimal adhesions at the second stage performed after 10 days. Further outcomes are described in Table I. Cillo et al[17] reported a case study in which they used the same first-stage technique, but they performed stage II laparoscopically, with resection of the diseased hemiliver through a 10-cm Pfannenstiel incision. The authors reported a 90% FLR growth over 9 days with no complications.

Associating liver tourniquet and portal ligation for stage hepatectomy (ALTPS). This variation uses a tourniquet to ensure parenchymal compression and cessation of blood flow across the future line of transection while avoiding a physical split. ALTPS has been described in 3 studies.[18-20] Robles et al[19] used a 1-cm deep groove to place and tighten a 3-mm Vicryl (V152; Ethicon, Somerville, New Jersey, USA) tourniquet, after which ultrasonography confirming occlusion of the vessels between the 2 hemilivers. This technique was termed ALTPS. The case series included 22 patients, in whom the authors reported a median FLR growth of 61% over 7 days and a morbidity of 27% and 36% for stage I and stage II, respectively (including all types of complications). Median hospital stay, including both surgical stages, was 16 days. Cai et al[20] reported a similar technique performed laparoscopically. They used a Flocare nasogastric tube (Nutricia Advanced Medical Nutrition, BG Schipol, Airport, The Netherlands) as a tourniquet with a guidewire inside and passed the ends through a thorax tube that was used to allow tightening during the laparoscopic procedure. The authors reported no postoperative bile leakage. Further outcomes for all techniques of a noncomplete physical split are summarized in Table I, and a comparison with the ALPPS registry data is provided.

Sequential ALTPS. Robles Campos et al[18] reported the use of ALTPS in conjunction with a delayed PVE for perihilar tumors to allow a "nontouch" approach to be followed with the aim of decreasing tumor spread, called sequential ALTPS. The first stage consisted of applying the tourniquet as described previously in ALTPS but without ligating the portal vein and performing PVE on the fourth day postoperatively. The authors hypothesized that the delayed cessation of blood flow may be related to a decreased impact and severity of venous congestion in the FLR, possibly attenuating the risk of postoperative liver failure. The patient described in this report was disease-free at 18 months, and further outcomes are included in Table I.

Use of ALPPS for salvage or rescue. ALPPS has been used as both a method of salvage for failed PVE and intraoperative rescue when the FLR is deemed too small after tumor clearance. Conversion to ALPPS appears successful after both PVE and PVL with acceptable clinical outcomes (Table II). Truant et al[27] reported the largest series of 9 patients, which showed no difference in major complications compared with subjects who had no PVE before an in situ split.

Specific considerations for preventing segment IV ischemia. Complete devascularization of segment IV has been reported to cause complications through ischemic necrosis and infection, which can be a worrisome cause of morbidity and mortality in ALPPS.[30,31] Some groups have advocated for the use of antibiotics between stages.[26,32-34] Alvarez et al[35] support their use to specifically decrease the risk of infection and reported no formation of an abscess or fistulae in segment IV. The same group also hypothesized that partial ALPPS had the potential to decrease ischemia to segment IV as the result of a smaller parenchymal split. Hernandez-Alejandro et al[36] recommended preserving the middle hepatic vein to prevent congestion in segment IV and to decrease the risk of ischemia. Resection of segment IV to avoid bile leak was performed by Andriani.[37]

Specific operative maneuvers (Pringle, hanging, anterior approach). There is intermittent reporting for the use of hilar vascular occlusion (Pringle) and hanging maneuvers during the first stage of ALPPS (Table III). Chan et al[41] supported the use of an anterior approach to enable ALPPS without hilar inflow occlusion or mobilization of the liver. This approach was hypothesized to minimize both adhesions encountered at the second stage and tumor dissemination. The authors reported minimal adhesions at the second stage and no long-term recurrences. Li et al[48] adopted a completely "nontouch" approach for advanced gall bladder carcinoma with tumor infiltration into the right or left portal vein. This technique involved an anterior approach without liver mobilization or hilar vascular occlusion; the side of the hepatoduodenal ligament containing the infiltrated branch of portal vein was not touched during the first stage. PVE was then performed 2 days postoperatively, which led to FLR hypertrophy

Table II. Studies including patients converted to ALPPS after PVE or intraoperative rescue after FLR deemed insufficient

Reference	*Indication*	n	*FLR after PVE or PVL*	*FLR after in situ split, %*	*Successful conversion (%)*
Bjornsson et al,[21] 2013 *Case Rep Surg*	Failed PVE	2	— 42 (% FLR growth)	106 (% FLR growth) 95 (% FLR growth	100
Conrad et al,[22] 2012 *Ann Surg*	Failed PVE	1	—	45 (% FLR growth)	100
Gauzolino et al,[23] 2013 *Updates Surg*	Failed PVE	1	25 (FLR/TLV)	32 (FLR/TLV)	100
Jackson et al,[24] 2014 *Case Rep Surg*	Intraoperative rescue	1	—	40–50 (FLR/TLV)	100
Lau et al,[25] 2015 *Ann Surg*	Intraoperative rescue	1	38 (FLR/TLV)	60 (FLR/TLV)	100
Nadalin et al,[26] 2014 *Z Gastroenterol*	Failed PVE	1	*	*	100
Truant et al,[27] 2015 *Eur J Sur Oncol*	Failed PVE	9	—	49 (Median % FLR growth after failed PVE)	—
Tschour et al,[28] 2013 *Eur J Sur Oncol*	Failed PVL (± PVE)	3	30 (sFLR) 25 (sFLR) 19 (sFLR)	47 (sFLR) 41 (sFLR) 37 (sFLR)	100
Vyas et al,[29] 2014 *J Gastrointest Cancer*	Failed PVE	1	23 (FLR/TLV)	43 (FLR/TLV)	100

*No individual outcomes reported for patient.
Outcomes stated as "FLR after in-situ split" measure growth from starting FLR before initial PVE/PVL, unless stated otherwise.
ALPPS, Associated liver partition and portal vein ligation for staged hepatectomy; *FLR*, future liver remnant; *PVE*, portal vein embolization; *PVL*, portal vein ligation; *sFLR*, standardized future liver remnant; *TLV*, total liver volume.

of 86% and 65% over 6 and 14 days post-PVE, respectively.

Use of a laparoscopic approach at either stage. The use of laparoscopy during both stages of ALPPS has been performed successfully.[9,17,20,22,27,38,49,52,56] On the basis of the small numbers available, there are subjective reports of decreased adhesions encountered after a laparoscopic first stage[17,38]; however, a laparoscopic approach is believed likely to be associated with an increase in technical difficulty.[38] The largest single series was published by Sodergren et al,[13] with 10 patients undergoing a laparoscopic first stage as part of the RALPP technique The recently published registry data contain 4 patients treated laparoscopically with no serious complications (CD ≥ IIIb).[1] Cillo et al[17] showed that an anterior approach with a hanging maneuver can be performed laparoscopically, which was combined with MWA as part of a totally laparoscopic ALPPS.

Method to identify biliary complications. Identifying leaks at the first stage was reported by the use of multiple methods, including the methylene blue test,[40,41] the "white test,"[26] and hydraulic testing.[9,19,35,44] Cholangiography was used commonly for the second stage.[33,35,44] Dokmak and Belghiti[45] ligated the bile duct in all patients in an effort to accelerate hypertrophy; however, they reported that 88% of patients developed biliary fistulas and bilomas from the transection surfaces. Robles et al[19] compared biliary complications in those with and without bile duct ligation. They showed rates of biliary complications in those with and without ligation were 40% vs 8%, respectively. Variations in dealing with segments IV and I during transection also may play a role in determining bile leaks. Li et al[47] reported that in patients with bile leaks, the segment IV bile duct was responsible. The authors put forward a recommendation to perform preoperative investigations of anatomy to identify variations biliary anatomy. Knoefel et al[46] recommended taking segment I consistently during right trisectionectomy, even if it had no tumor infiltration, because this would aid bile duct preparation during transection and decrease potentially the risk of bile leakage.

Use of a bag or protective film to contain the diseased hemiliver. The method of containing the diseased hemiliver or covering of the transection surfaces varies widely. Commonly, a plastic bag or

Table III. Summary of the technical variations for included papers

					Laparoscopic		*Biliary system*			
Author	*Year*	*Journal*	n	*Resection type(s)*	*Stage 1*	*Stage 2*	*Stage 1*	*Stage 2*	*Containment of DH and transection surfaces*	*Maneuvers*
Schnitzbauer et al,[2] (original description of ALPPS)	2012	*Ann Surg*	25	R trisectionectomy + Sg 1 or + SubSg 2	—	—	—	—	Plastic bag	Pringle ($n = 6$)
Alvarez et al[9]	2015	*Ann Surg*	30	R hepatectomy R trisectionectomy L trisectionectomy	Yes ($n = 1$)	Yes ($n = 1$)	Hydraulic test, cholangiography	—	Plastic bag or sheath	Intermittent pringle (n = 9)
Alvarez et al[35]	2013	*J Gastrointest Surg*	15	R hepatectomy R trisectectionectomy L trisectectionectomy	—	—	Cholecystectomy, hydraulic testing, cholangiography	Cholangiography	Plastic bag	Intermittent pringle ($n = 5$)
Andriani[37]	2012	*Ann Surg*	2	R trisectionectomy	—	—	—	—	Plastic bag	—
Bjornsson et al[21]	2013	*Case Rep Surg*	2	R trisectionectomy R hepatectomy	—	—	—	—	Plastic bag	No pringle
Brustia et al[38]	2013	*J Am Coll Surg*	6	R hepatectomy R trisectionectomy	Yes ($n = 1$)	Yes ($n = 1$)	—	—	Type I acellular collagen membrane, TachoSil sponges	Hanging (n = 3), Anterior approach
Cai et al[20]	2014	*J Laparoendosc Adv Surg Tech A*	1	R hepatectomy	Yes ($n = 1$)	Yes ($n = 1$)	—	—	—	—
Cavaness et al[39]	2013	*J Gastrointest Surg*	1	R trisectionectomy + Sg 1	—	—	—	—	Plastic bag	—
Chan et al[40]	2014	*World J Gastroenterol*	1	R trisectionectomy	—	—	Methylene blue test	—	None	Anterior approach
Chan et al[41]	2014	*Ann Surg*	1	R trisectionectomy	—	—	Methylene blue test	—	None	No Pringle, Anterior approach
Chia et al[42]	2014	*Int J Surg Case Rep*	1	R trisectionectomy	—	—	Cholecystectomy, "leak" test	—	None	No Pringle, Anterior approach

(*continued*)

Table III. (*continued*)

					Laparoscopic		*Biliary system*			
Author	*Year*	*Journal*	n	*Resection type(s)*	*Stage 1*	*Stage 2*	*Stage 1*	*Stage 2*	*Containment of DH and transection surfaces*	*Maneuvers*
Cillo et al[17]	2015	*Ann Surg Oncol*	1	R trisectionectomy	Yes ($n = 1$)	Yes ($n = 1$)	Cholecystectomy			No Pringle
Conrad et al[22]	2012	*Ann Surg*	1	R trisectionectomy + Sg 1	Yes ($n = 1$)	—	—	—	Plastic sheath	—
de Santibanes et al[43]	2012	*World J Surg*	3	R hepatectomy R trisectionectomy	—	—	—	—	—	—
de Santibanes et al[44]	2014	*J Am Coll Surg*	2	R hepatectomy + Sg 2,3	—	—	Cholecystectomy, hydraulic test, cholangiography	Cholangiography, hydraulic test	Plastic sheath between cut surfaces	Pringle ($n = 2$), Hanging ($n = 2$)
Dokmak and Belghiti[45]	2012	*Ann Surg*	8	R trisectionectomy R hepatectomy	—	—	Bile duct ligation ($n = 8$)	—	—	—
Gall et al[12]	2015	*Ann Surg*	5	R hepatectomy	Yes ($n = 4$)	—	—	—	—	—
Gauzolino et al[23]	2013	*Updates Surg*	4	R trisectionectomy R hepatectomy L hepatectomy + Sg 1	—	—	—	—	Plastic bag	Hanging, Pringle ($n = 1$)
Gringeri et al[16]	2015	*Ann Surg*	1	R trisectionectomy – Sg 1	Yes ($n = 1$)	—	—	—	—	—
Herman et al[34]	2015	*J Gastrointest Cancer*	7	R hepatectomy R trisectionectomy	—	—	—	—	Adhesion barrier film	—
Hernandez-Alejandro et al[36]	2014	*Surgery*	14	R trisectionectomy	—	—	—	—	Plastic bag ($n = 4$)	—
Ielpo et al[32]	2013	*Hepatogastroenterology*	6	R trisectionectomy ± Sg 1	—	—	—	—	Fibrin sealant	—
Jackson et al[24]	2014	*Case Rep Surg*	1	R hepatectomy	—	—	Cholecystectomy	—	Argon beam coagulation, fibrin glue, plastic wrapping	Intermittent Pringle

(*continued*)

Table III. (*continued*)

					Laparoscopic		*Biliary system*			
Author	*Year*	*Journal*	n	*Resection type(s)*	*Stage 1*	*Stage 2*	*Stage 1*	*Stage 2*	*Containment of DH and transection surfaces*	*Maneuvers*
Knoefel et al[46]	2013	*Br J Surg*	7	R trisectionectomy + Sg 1	—	—	Cholecystectomy	—	Plastic bag (stage 1), haemostatic sponge (stage 2)	—
Lau et al[25]	2014	*Ann Surg*	1	R hepatectomy	—	—	—	—	Seprafilm adhesion barrier	Anterior Approach
Li et al[47]	2013	*J Gastrointest Surg*	9	R trisectionectomy	—	—	—	—	Plastic bag or silicone sheeting	—
Li et al[48]	2016	*Ann Surg*	2	R trisectionectomy	—	—	—	—	Drains to separate transection surfaces	Anterior approach, non-touch (PVE on POD 2)
Machado et al[49]	2012	*Ann Surg*	1	R hepatectomy	Yes ($n = 1$)	Yes ($n = 1$)	—	—	—	—
Machado et al[50]	2013	*Ann Surg Oncol*	1	R trisectionectomy + Sg 1, 2 – Sg 4b	—	—	—	—	Bioactive sealant	—
Nadalin et al[26]	2014	*Z Gastroenterol*	15	R trisectionectomy ± Sg 1	—	—	Cholecystectomy "White test" for bile leakage	—	Silicone sheeting	Hanging
Oldhafer et al[51]	2014	*World J Surg*	7	R hepatectomy – Sg 1 or + Sg 4b or + Sg 2/4a, 3 R trisectionectomy + Sg 2 or + Sg 2/3	—	—	T-tube placed in common bile duct	—	Plastic bag (n = 2) Collagen fleece (n = 8)	Hanging
Petrowsky et al[10]	2015	*Ann Surg*	6	R hepatectomy R trisectionectomy L trisectionectomy	—	—	—	—	—	Anterior approach

(*continued*)

Table III. (*continued*)

Author	Year	Journal	n	Resection type(s)	Laparoscopic		Biliary system		Containment of DH and transection surfaces	Maneuvers
					Stage 1	Stage 2	Stage 1	Stage 2		
Ratti et al[30]	2014	*Updates Surg*	8	R hepatectomy R trisectionectomy ± Sg 1	—	—	MRCP preoperatively, if dilation or obstruction in right biliary tree also performed PTBD	—	Bioactive sealant	Intermittent Pringle
Robles Campos et al[18]	2014	*Cir Esp*	1	R trisectionectomy	—	—	—	—	—	Nontouch (PVE on POD 4)
Robles et al[19]	2014	*Br J Surg*	22	R trisectionectomy R hepatectomy	—	—	Cholecystectomy, cholangiography, bile duct ligation (n = 10)	—	—	No Pringle (second stage), Hanging (n = 7)
Sala et al[33]	2012	*Updates Surg*	10	R hepatectomy R trisectionectomy L trisectionectomy	—	—	—	Cholangiography, hydraulic test	Plastic bag	Intermittent Pringle (n = 2)
Sodergren et al[13]	2015	*HPB (Oxford)*	12	R hepatectomy	Yes (n = 10)	—	—	—	—	—
Tanaka and Endo[31]	2015	*Ann Surg*	7	R trisectionectomy						
Torres et al[52]	2013	*Arq Bras Cir Dig*	39	R trisectionectomy	Yes (n = 2)	Yes (n = 2)	—	—	Fibrin sealant (n = 18), plastic bag (n = 8)	—
Troja et al[53]	2014	*Int J Surg*	5	R trisectionectomy ± Sg 2, 3 Segmentectomy 4, 5, 8 + SubSg 3	—	—	—	—	—	—
Truant et al[27]	2015	*Eur J Surg Oncol*	62	R hepatectomy R trisectionectomy Other	Yes (n = 2)	—	T-tube (n = 3), Bile duct ligation (n = 6)	—	—	—

(*continued*)

Table III. (*continued*)

					Laparoscopic		*Biliary system*			
Author	*Year*	*Journal*	n	*Resection type(s)*	*Stage 1*	*Stage 2*	*Stage 1*	*Stage 2*	*Containment of DH and transection surfaces*	*Maneuvers*
Tschuor et al[28]	2013	*Eur J Surg Oncol*	3	R trisectionectomy	—	—	—	—	—	—
Vennarecci et al[54]	2014	*Eur J Surg Oncol*	3	R hepatectomy R trisectionectomy	—	—	Cholecystectomy, Trans-cystic tube, Biliostasis test	—	Fibrin sealant	Anterior approach, Pringle, Hanging
Vennarecci et al[55]	2014	*World J Surg*	2	R hepatectomy	—	—	—	—	None	Anterior approach (n = 1), Hanging (n = 2)
Vyas et al[29]	2014	*J Gastrointest Cancer*	1	R hepatectomy	—	—	T-tube	—	—	—
Xiao et al[56]	2014	*Surg Endosc*	1	R hepatectomy	Yes (n = 1)	Yes (n = 1)	Cholecystectomy	—	Haemostatic materials on surface	Anterior approach, Hanging

Resections were classified by use of the Brisbane 2000 nomenclature. [57]

ALPPS, Associated liver partition and portal vein ligation for staged hepatectomy; DH, Diseased Hemi-liver; *L*, left, *MRCP*, Magnetic Resonance Cholangiopancreatography; *POD*, postoperative day; *PTBD*, percutaneous transheptic biliary drainage; *PVE*, portal vein embolization; *R*, right; *Sg*, segment; *SubSg*, subsegment.

sheath is used to contain the diseased hemiliver (Table III). Other methods reported include applying fibrin glue to the transection surfaces, the use of acellular collagen membranes, argon beam coagulation, or a combination of methods detailed in Table III. The use of a plastic bag in the first stage has raised concerns regarding unnecessary laparotomies for failure of progression to stage II and acting as a potential source of infection.[41] Chan et al[40,41] supported the use of no bag or protective film made viable by the anterior approach and the use of methylene blue testing in the first stage to detect bile leak. Troja et al[53] reported performing an omentoplasty on 2 patients in an attempt to decrease adhesions and biliary complications.

Number and position of resected segments. Because ALPPS has allowed the rapid growth of what would have been considered too small for size FLR, many variations and types of resections have been performed successfully (Table III), including hemihepatectomies or trisectionectomies of both the left and right liver. ALPPS also has allowed surgeons to go beyond what was considered possible previously with 2-stage hepatectomy, allowing an increase in the number of segments resected and a decrease in the size of FLR immediately after stage I. Examples include resections leaving the FLR consisting of only segments I and IV,[44] segments I and IVb,[51] and monosegmental FLRs.[9]

DISCUSSION

Since the original description by Schnitzbauer et al,[2] the ALPPS technique has taken many routes, sparking both intense enthusiasm as well as skepticism alike among the surgery community. It is still unclear where the technique should fit within the surgeon's armament. This review outlines the main technical variations in the ALPPS technique as well as relevant clinical outcomes. The most important contribution of ALPPS is the rapid hypertrophy of liver parenchyma FLR and, therefore, the acceptance of a decrease in the estimated size of the FLR required to avoid posthepatectomy liver failure. ALPPS has enabled larger resections, and even the acceptance of a monosegmental FLR (because of its expected hypertrophy)[9] to become a possibility.[58] This increase in hypertrophy of the FLR raises the threshold for what is considered resectable, theoretically decreasing the proportion of patients who do not reach second stage.

Despite this enthusiasm, there is a lack of evidence to guide clinicians about the most appropriate role for ALPPS in liver surgery. To date, there is no Level 1 evidence that illustrates the benefit of ALPPS over PVE and 2-stage resections, and with a greater number of technical variations emerging, meaningful comparisons of clinical outcomes are difficult to make. To our knowledge, the only registered, randomized controlled trials recruiting currently are the Scandinavian multicenter Liver Growth Stimulation in Advanced Colorectal Liver Metastatic Disease (LIGRO) trial (ALPPS vs PVE) and the Regeneration of Liver: Portal Vein Embolization Versus Radiofrequency Assisted Ligation for Liver Hypertrophy (REBIRTH) trial from Imperial College London (RALPP vs PVE).

Containment of the transection surfaces and the diseased hemiliver remains a point of contention, offering both potential advantages and downfalls. The primary aim of containment is to decrease the formation of adhesions between stages I and II and to contain bile leakage from the transection surfaces. The use of a plastic bag to contain the diseased hemiliver or a plastic sheath between transection surfaces is well described, but in situations in which a patient is not able to progress to the second stage, these plastic foreign bodies cannot be left in situ long term and require removal operatively. Bioactive sealants, such as fibrin and acellular collagen membranes, have been used to prevent adhesions and bile ducts without leaving a foreign body within the abdomen. Not containing the transection surfaces or diseased hemiliver is increasingly popular, with some groups recommending the use of an anterior approach to avoid mobilization of the liver and hence, theoretically, to decrease the risk of adhesions.[25,40,41,48,55] Bile leaks are a clinically important source of complications within ALPPS and can lead to serious morbidity secondary to sepsis.[19] Avoiding ligation of the bile duct at the first stage may be beneficial in decreasing biliary fistulae and leakage from the cut surface. A variety of techniques to identify bile leaks at the first stage are used; however, data relating to efficacy in decreasing complications are lacking.

Technical variations to splitting the liver, such as RALPP[12] and LAPS,[13] offer advantages in this regard, because transection is performed through an avascular groove in the second stage without the need for containment of any transection surface between stages. Furthermore, the majority of patients are able to leave hospital before the second stage, thereby decreasing overall costs of the 2-stage procedure. Laparoscopic surgery is well known to be associated with a decrease in adhesions, operative trauma, and postoperative duration of stay[59,60]; however, any benefit is still uncertain regarding its use in ALPPS, and these techniques

should be limited to experienced centers. Larger controlled studies are still required before any potential advantages of a laparoscopic first stage in a 2-stage procedure can be determined.

The recently published registry data reported a link between the Pringle maneuver and decreased FLR hypertrophy. This systematic review has shown that reported use of this and other maneuvers throughout the literature is not consistent. Therefore, we would recommend standardized reporting of these maneuvers in future trials, including quantification of implementation given their potential impact on FLR growth. The anterior approach also may be associated with improved oncologic outcomes[41] and has been performed in 37% of ALPPS patients.[57] Segment IV is believed to be a source of potentially severe complications if left to become ischemic, acting as a source of sepsis. This review found that a variety of ways are used to try and prevent this ischemia, such as resection of segment IV at the first stage[37] or providing antibiotics to decrease the risk of infection.[35] Avoiding a physical or complete split in the liver may help decrease the devascularization segment IV, because avoiding a complete split potentially limits the loss of blood supply and decreases the segmental surface area open to infection. Management of the vascular supply to segment IV and bile duct during the first stage should be given detailed consideration to limit associated complications. In general, reporting ischemia and necrosis of segment IV is poor, and the inclusion of such effects in segment IV in further studies may help guide improvements in preventing such complications.

ALPPS as a tool for PVE salvage or intraoperative rescue has been suggested by some as the only indication that justifies the current morbidity and mortality rates associated with the procedure.[22] Current evidence shows that salvage ALPPS is a successful approach. Truant et al[27] showed that previous PVE did not affect short-term morbidity or mortality rates; however, there remains a potential for poorer long-term oncological outcomes as a result of delay.

Multiple alternatives to performing a complete physical split have been described. A major motivation behind these alterations is a continual effort to decrease the morbidity associated with ALPPS. As demonstrated in Table I, avoiding a complete parenchymal transection does not necessarily jeopardize the rate and volume of hypertrophy and decreases the morbidity and mortality rates described in early series. The publication of the data in the ALPPS registry does not report morbidity separately for either stage, preventing a detailed comparison with the variant ALPPS morbidity profiles. Techniques for partial splitting of the liver[9,10] have yielded promising results in decreasing morbidity, and a complete transaction has shown to be an independent risk factor for complications in comparison with a partial split.[9] Avoiding division of hepatic parenchyma at the first stage, as demonstrated in RALPP,[13,14] LAPS,[16,17] and ALTPS,[18,19] has potential beneficial effects on limiting complications, including blood loss at both stages. Interestingly, Robles et al[19] reported a 23% rate of biliary complications after stage II when using a tourniquet. Both the use of a tourniquet and ablation achieve vascular occlusion; however, transection through a previously formed avascular grove in LAPS and RALPP may decrease the risk of a biliary fistula and subsequent abdominal infection.

Reported second-stage morbidity of CD $\geq$ IIIb for partial ALPPS, RALPPS, and ALTPS was 33%, 10%, and 9%, respectively. First-stage operative time also was decreased markedly in variations that did not physically split the liver compared with the registry data, with reported operating times of 120–170 minutes[16-19] and 327 minutes,[1] respectively. As shown in Table I, FLR hypertrophy across all variations ranged between 60[10] and 90%.[9] The registry data reported a median FLR hypertrophy of 80%, demonstrating that the rapid FLR hypertrophy associated with ALPPS is preserved largely when using alternatives to a physical split; this observation was based on limited data and highlights the increasing need for randomized controlled trials to make meaningful comparisons. Furthermore, these techniques may not be feasible in a mono- or bisegmental FLR or where bilioenteric anastomosis or vascular resections are required.

In conclusion, ALPPS has revolutionized liver surgery, changing the landscape of patient eligibility and acting as a catalyst for the novel application of existing technologies and concepts. The current literature demonstrates a large variability in the techniques of ALPPS that limits meaningful statistical comparisons of outcomes. There is marked heterogeneity in the types of operations performed and the subtleties of operative technique. Most variations are at an early stage, yet they may play a role in decreasing morbidity and mortality such that a physical parenchymal split may become unnecessary in the pursuit of rapid FLR hypertrophy. Current evidence suggests the mechanism behind such rapid hypertrophy to be associated with a systemic

response and adds weight to the argument of avoiding a complete physical split.[7]

There is a need for further basic science trials to identify the exact biochemical mechanisms involved. There is also a clear need for randomized controlled trials to allow meaningful comparisons of clinical outcomes and demonstrate both the safety and efficacy of ALPPS and its variations. The recent registry data[1] further demonstrate the need to take patient demographic and tumor configuration into account in future study designs, because an optimal ALPPS variation or approach is unlikely to be "one size fits all" and will depend on anatomical, oncologic, and patient factors.

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