



# Preparing for liver surgery with “Alphabet Soup”: PVE, ALPPS, TAE-PVE, LVD and RL

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**Contributions:** (I) Conception and design: All authors; (II) Administrative support: DC Madoff; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Abstract:** Future liver remnant (FLR) size and function is a critical limiting factor for treatment eligibility and postoperative prognosis when considering surgical hepatectomy. Pre-operative portal vein embolization (PVE) has been proven effective in modulating FLR and now widely accepted as a standard of care. However, PVE is not always effective due to potentially inadequate augmentation of the FLR as well as tumor progression while awaiting liver growth. These concerns have prompted exploration of alternative techniques: associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), transarterial embolization-portal vein embolization (TAE-PVE), liver venous deprivation (LVD), and radiation lobectomy (RL). The article aims to review the principles and applications of PVE and these newer hepatic regenerative techniques.

**Keywords:** Hepatic regeneration; future liver remnant; embolization

Submitted Jul 30, 2019. Accepted for publication Sep 10, 2019.

doi: 10.21037/hbsn.2019.09.10

**View this article at:** <http://dx.doi.org/10.21037/hbsn.2019.09.10>

## Introduction

Extended hepatectomy with curative intent is widely utilized in patients with a variety of primary and secondary liver diseases. Recent advancements in surgical technique and peri-operative management have enabled more aggressive resection, leaving the size of the future liver remnant (FLR) as one of the most critical determinants of treatment eligibility and postoperative prognosis (1).

The prodigious regenerative capacity of the human liver is now well-established (2-5). In 1897, Sir James Cantlie first documented the concept of the atrophy-hypertrophy complex in autopsy observations made in a patient with injury to the right hepatic lobe (2,6). Compensatory hypertrophy after bile duct or portal vein occlusion was demonstrated in animal experiments as early as the first half of 20<sup>th</sup> century (7,8). In 1986, Kinoshita *et al.* first described the possibility of broadening resection candidacy through compensatory liver enlargement achieved via portal vein embolization

(PVE), although the original intention was to treat portal tumor thrombi in the setting of hepatocellular carcinoma (9). Shortly thereafter in 1990, Makuuchi *et al.* reported the first series on PVE, performed in 14 patients with hilar cholangiocarcinoma, demonstrating the safety and feasibility of the technique in decreasing post-resection liver failure (10).

Pre-operative PVE is now accepted as standard of care for patients undergoing partial hepatectomy. However, the potential for inadequate augmentation of the FLR as well as tumor progression while awaiting liver growth have prompted exploration of alternative techniques. Newer strategies have recently been developed, chief among them associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), transarterial embolization-portal vein embolization (TAE-PVE), liver venous deprivation (LVD), and radiation lobectomy (RL) (11-13). This article summarizes the principles and applications of these techniques by reviewing available observational and

experimental data.

### Physiology of liver regeneration

In the absence of an inciting event or injury, less than 0.01% of normal hepatocytes are actively dividing at any point (2,3,14,15). Upon hepatic injury, however, there is a dramatic increase in hepatocyte proliferation, mediated by the release of multiple growth factors, which continues for about 14 days (3,15). Because the regenerative process depends upon the proliferation of the remaining uninjured hepatocytes, the regenerative rate and capacity in chronically diseased livers is lower than that in healthy livers (16-19). Multiple changes within the portal venous system are thought to initiate the regenerative process. In the case of partial hepatectomy, resection results in a sudden increase in portal venous inflow within the remaining liver while the arterial supply remains unchanged (15,20). Consequently, the liver experiences an increase in both portal venous pressure and delivery of intestinally-derived growth factors while simultaneously experiencing decreased oxygen delivery secondary to a relative increase in the ratio of portal venous to arterial blood supply (2,3,14,15,18). The resulting alterations in endothelial stress, vascular permeability, growth factor delivery, and oxygen tension trigger a regenerative pathway which closely resembles that which occurs during the typical wound-healing process.

At the molecular level, numerous growth factors and signaling pathways are involved in hepatocyte activation and hyperplasia, as reflected by animal studies demonstrating upregulation of more than 100 genes within a few hours of hepatic resection (21,22). The hepatocyte-specific mitogen hepatocyte growth factor (HGF) is stored in the extracellular matrix of the liver and is released upon tissue injury, resulting in a delayed genetic response (3,15,21). Intestinally-derived trophic factors such as epidermal growth factor (EGF) are delivered to the injured liver in greater concentration secondary to augmented portal inflow, as previously described (15,22,23). Finally, global trophic hormones such as insulin appear to play a synergistic role in hepatocyte stimulation as slower rates of FLR growth have been observed in diabetic patients (16,24).

### Estimation of future liver remnant (FLR), kinetic growth rate (KGR) and quantitative liver function

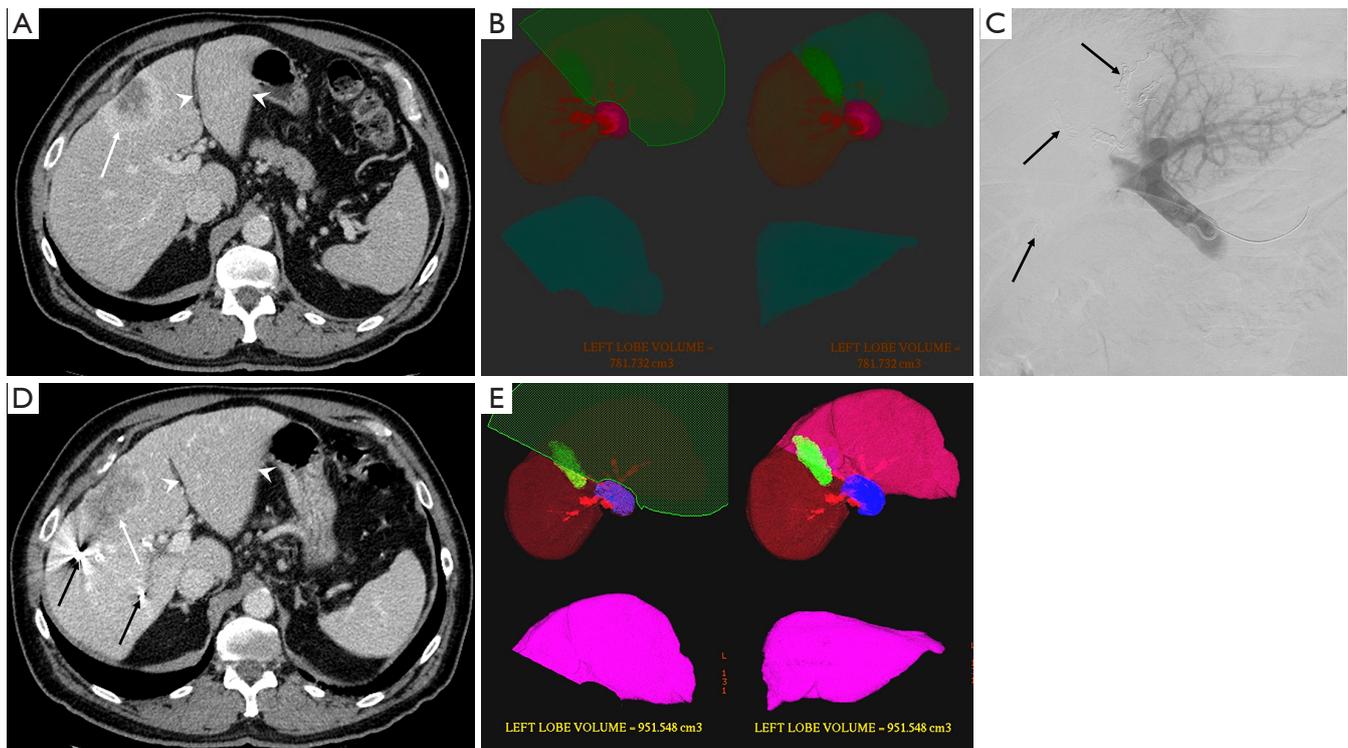
Accurate estimation of FLR size is critical when planning hepatectomy and establishing the need for preoperative

hepatic augmentation. The FLR is typically measured on cross-sectional imaging, most commonly using computed tomography (CT) (*Figure 1*). Because liver volume directly correlates with body size (25), normalization of the FLR to total liver volume (TLV), termed standardized FLR (sFLR), has been suggested and clinically validated (26,27). Total estimated liver volume (TELTV) is calculated using the following formula:  $TELTV = -794.41 + 126.28 \times BSA$  (where BSA is body surface area) (26,27). This formula was derived utilizing data from 292 subjects obtained in four centers in North America and Europe and had been shown to be accurate in estimating the TLV (1,26-28). Alternatively, the TLV can be calculated using CT volumetry, but this technique adds empirical measurement errors and tends to over-estimate FLR size due to a degree of liver atrophy which occurs as a result of pre-operative regenerative interventions (29).

The FLR volume required for safe liver resection varies with the underlying liver health. An FLR greater than 20% is generally considered safe for hepatectomy in patients without liver disease (27,30-32). In liver injured by chemotherapy, steatosis, infection, or other iatrogenic injury, a threshold of 30% is recommended to minimize the risk of post-operative liver failure (33-36). In patients with severe liver disease, including those with cirrhosis, a minimum of 40% is desired (1,33,34).

KGR is an alternative predictor of post-resection liver failure following PVE (37). It refers to hypertrophy per time after PVE and has been shown to better predict both post-resection liver insufficiency and mortality as compared to sFLR. In a study of 107 subjects undergoing right hepatic PVE and subsequent hepatectomy, Shindoh *et al.* reported no liver failure or deaths in the 68 patients with KGR greater than 2% per week (37).

Clearance of indocyanine green (ICG) has been used as a biochemical surrogate for global quantitative liver function and shown to be predictive of outcomes when utilized in conjunction with FLR, particularly in patients with cirrhosis (38-40). More recently, technetium-99m-mebrofenin hepatobiliary scintigraphy (HBS) (41-43) and technetium-99m-diethylenetriaminepentaacetic acid-galactosyl human serum albumin single photon emission computed tomography (GSA SPECT) (41,44,45) were introduced and utilized in order to accurately account for heterogeneous hepatic functionality in case of prior insults or intervention to the part of the liver, for example, portal tumor thrombus or regional biliary obstruction. Lastly, the liver function estimate based on magnetic resonance imaging (MRI) with



**Figure 1** A 71-year-old man with intrahepatic cholangiocarcinoma who underwent right portal vein embolization (PVE) for small projected future liver remnant (FLR). (A) Pre-procedural contrast-enhanced CT showing the tumor (arrow) and left hepatic lobe (arrowheads); (B) pre-procedural 3D CT volumetry demonstrating segmentation (upper left) and isolation (upper right) of the left hepatic lobe with analysis of volumes (bottom left and right); (C) patient underwent right hepatic PVE with coils (arrows); (D) post-procedural contrast-enhance CT showing the tumor (white arrow), coils (black arrows), and hypertrophy of the left hepatic lobe (arrowheads); (E) post-procedural 3D CT volumetry confirms increase in left hepatic lobe volume.

Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) demonstrates promising results with on-going investigation (46-48).

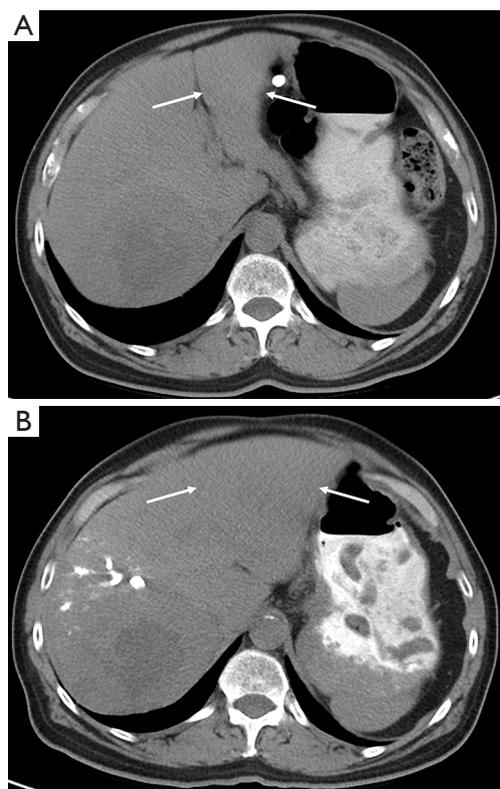
### PVE

PVE is the mainstay of preoperative liver augmentation and substantial data confirming its safety and efficacy have accrued since it was first performed over 30 years ago. The procedure is indicated when the expected FLR is too small to provide adequate function. It is performed on the tumor-bearing liver to promote hypertrophy of the unaffected lobe, and is most effective when there is complete occlusion of the treated portal veins without the opportunity for recanalization or collateral formation (49) (Figure 2).

Access to the portal system is typically obtained via percutaneous transhepatic puncture. Either ipsilateral or contralateral approaches may be taken (in reference to the segment of tumor-bearing liver), with arguments in favor

of each. The ipsilateral approach minimizes the risk of inadvertent injury to the FLR during PVE and provides easier access to the segment 4 portal veins if an extended right hepatectomy is planned (50,51) (Figures 3,4). However, as embolic material is administered in a retrograde manner, care in catheter manipulation is essential once embolization has begun so as to prevent disruption of embolic material and consequent non-target embolization. Use of reverse curve and balloon occlusion catheters as well as placement of coils or plugs has been described for this approach (50-52). The contralateral approach has the advantages of facilitating cannulation and antegrade embolization of right portal vein branches, although iatrogenic injury to the FLR and difficult segment 4 access remain concerns. Thus far, comparisons between the two techniques have demonstrated equivalent efficacy and complication rates (32,50,52-54). As such, selection is usually dictated by operator preference and the need for treatment of segment 4.

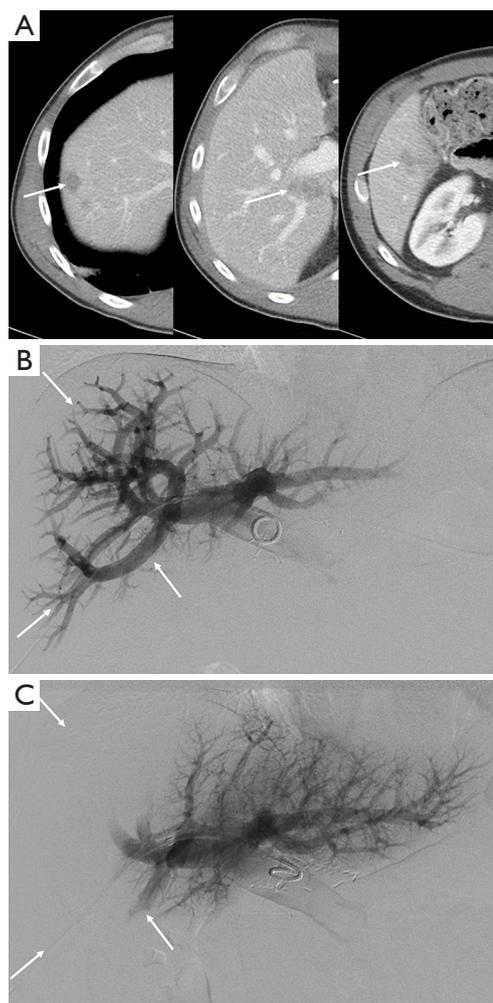
A variety of embolic materials have been utilized,



**Figure 2** A 54-year old man with hepatocellular carcinoma who underwent right portal vein embolization (PVE) with lipiodol for small projected future liver remnant (FLR). Pre- (A) and post- (B) embolization CT scans demonstrate significant increase in the volume of the left hepatic lobe (between arrowheads).

including polyvinyl alcohol (PVA), ethanol, microspheres, polidocanol, fibrin glue, lipiodol, and N-butyl-2-cyanoacetate (NBCA), as well as coils and plugs (51,55-58). Among these, NBCA and the combination of coils and particles are the most widely used. The combination of coils and particles has been shown to be safe and effective in ensuring both proximal and distal embolization but at the expense of higher cost than when other materials are used (58). NBCA is both highly effective and substantially cheaper, but induces a peri-portal inflammatory reaction which can result in both a post-embolization syndrome and periportal fibrosis (55-58). Additionally, proficient use of NBCA can be challenging for the inexperienced interventionalist.

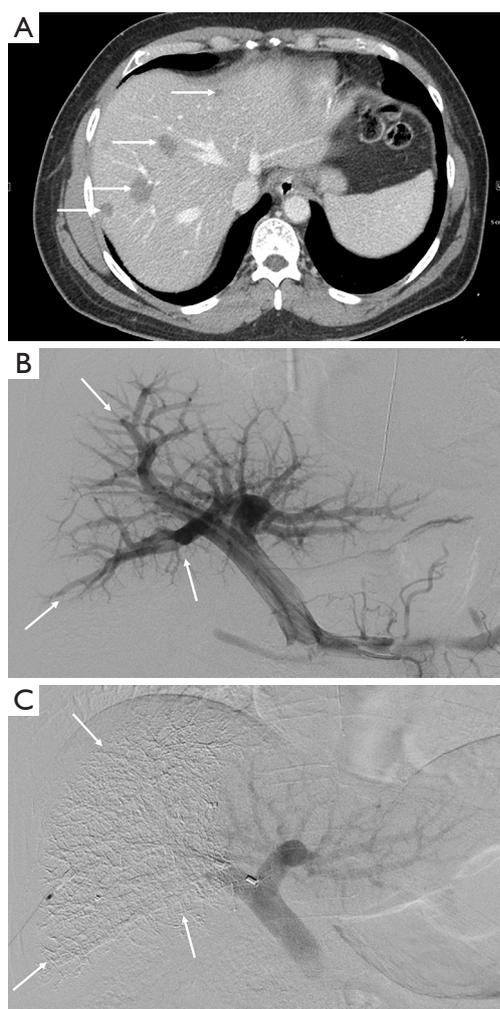
Reported technical success rates consistently reach greater than 95% regardless of the approach taken or embolic used (9,10,32,51,53,56-60) (Table 1). In the most recent systematic reviews and meta-analyses, mean FLR hypertrophy rates were reported to be 37.9–49.4% and



**Figure 3** A 46-year-old man with metastatic colon cancer status post multiple hepatic wedge resections and hepatic arterial infusion pump placement, now planned for right hepatectomy and referred for pre-operative portal vein embolization due to small projected future liver remnant (FLR). (A) Pre-procedural contrast-enhanced CT showing multifocal tumor (arrows) in the right hepatic lobe; (B) digital subtraction angiogram (DSA) demonstrating the pre-embolization appearance of the portal tree (arrows); (C) post-embolization DSA showing absence of filling in the right side of the portal tree (arrows).

rates of successful hepatectomy were 75.9–96.1% (59,61,62). Major complications occur in 2.2–3.1% of cases, and mortality is less than 0.1% (59,61,62) (Table 1).

The most commonly cited limitation to PVE is the potential for disease progression in the interval between embolization and resection. Some authors hypothesize that, in addition to the baseline rate of tumor growth,



**Figure 4** A 63-year-old man with metastatic colon cancer, planned for right hepatectomy and referred for pre-operative portal vein embolization due to small projected future liver remnant (FLR). (A) Pre-procedural contrast-enhanced CT showing multifocal tumor in the right hepatic lobe (arrows); (B) DSA demonstrating the pre-embolization appearance of the portal tree (arrows); (C) After embolization with lipiodol, DSA confirms absence of filling in the right side of the portal tree (arrows).

accelerated tumor progression may occur as a result of trophic factor release following PVE (63,64). Several of the newer strategies described below are designed to prevent this progression by accelerating the rate of hypertrophy, controlling existing tumor, or both.

### ALPPS

ALPPS is a surgical technique for FLR augmentation which

was first described in 2012 (65). It consists of concurrent surgical portal vein ligation (PVL) and in-situ separation of the tumor-bearing liver from the FLR prior to eventual resection. Like PVE, the procedure induces FLR growth via deprivation of portal supply to the tumor-bearing liver, but it was hoped that it would produce more rapid and extensive FLR augmentation through more complete portal occlusion as well as elimination of collateral portal flow from the FLR into the diseased segment.

The initial description of the procedure performed in 25 patients by Schnitzbauer *et al.* demonstrated markedly accelerated mean FLR hypertrophy rates of 75% within a median of 9 days, albeit with high associated mortality and morbidity (12% and 44%, respectively) (65). Subsequent studies and meta-analyses have consistently demonstrated FLR hypertrophy rates of 68–80% within 7 days (66–68) (Table 2). A recent meta-analysis comprising a total of 657 subjects with colorectal liver metastasis (CRLM) found a significantly greater KGR compared to isolated PVE/PVL (mean difference 19.07 mL/day), although there was no significant difference in the ultimate size of the FLR (71). A randomized controlled trial performed in 97 patients with CRLM reported significantly higher rates of successful resection in patients who had undergone ALPPS compared with PVE/PVL (92% *vs.* 57%); in fact, 12 of the 13 PVE/PVL patients who achieved insufficient FLR growth were subsequently successfully treated by ALPPS (67).

The main limitation to the technique is its substantial associated morbidity and mortality. Although decreased when compared to earlier studies (65,69,70), the 90-day mortality rate remains 8–9% (66,67) and both mortality and morbidity are elevated in comparison with PVE (68,71). These findings were initially attributed to the increased invasiveness of the procedure and consequent bile leakage, which complicated 20% of the cases reported by Schnitzbauer *et al.* (65). However, subsequent analysis of 320 subjects registered an international ALPPS database revealed that 75% of 90-day mortality was in fact due to post-stage 1 liver failure, despite 82% of patients achieving the goal FLR (66,72). This finding prompted consideration of volume-function dissociation as a potential cause for the liver failure, and further emphasized the importance of liver function analysis before performance of stage 2 resection (73,74). Histologic analysis of the post-ALPPS FLR demonstrated immaturity of both hepatocytes and the supporting stroma, which was not observed to comparable extent in the post-PVE FLR (75,76). In light of these findings, several modified versions of ALPPS have been proposed in an attempt to

**Table 1** Summary of meta-analysis and systematic reviews on PVE

Author, year	Type	# included studies/patients	Morbidity/mortality of PVE (%)	FLR increase (%)	Rates of successful resection (%)	Morbidity/mortality post-resection (%)	Difference between ipsilateral/contralateral transhepatic approach	Difference between the choice of embolic
Abulkhair <i>et al.</i> , 2008 (59)	Meta-analysis	37/1,088	2.2/0	8-27 (DH)	85	16/1.7	None	None
Wajswol <i>et al.</i> , 2018 (60)	Meta-analysis and Systematic Review	18/607	3.1/not reported	49.4 (RH)	75.9	23.2/1.2	None	None
Isofordink <i>et al.</i> , 2017 (61)	Meta-analysis and Systematic Review	17/1,953	3.9/not reported	43.2 (RH)	Not reported	Not reported/3.8	Not reported	Not reported
van Lienden <i>et al.</i> , 2013 (62)	Meta-analysis and Systematic Review	44/1,791	2.5/0.1	37.9 (RH)	80	10.4/3.3	Not reported	NBCA with greater FLR increase than gelfoam, PVA and fibrin glue

PVE, portal vein embolization; FLR, future liver remnant; DH, degree of hypertrophy; RH, relative hypertrophy; NBCA, N-butyl cyanoacrylate; PVA, polyvinyl alcohol.

**Table 2** Summary of meta-analysis and systematic reviews on ALPPS

Author, Year	Type	# included patients	FLR increase (%)	Rates of complete ALPPS (%)	Morbidity (%) (> Clavien-Dindo 3a)	Mortality (%)	Remarks
Schnitzbauer <i>et al.</i> , 2012 (65)	Retrospective cohort study	25	74 (RH)	100	44	12 (during index admission)	
Knoefel <i>et al.</i> , 2013 (69)	Prospective cohort study	7	63 (RH)	100	71.4	14.3 (7 days)	
Nadalin <i>et al.</i> , 2014 (70)	Retrospective cohort study	15	87.2 (RH)	100	66.7	28.7 (within 36 days)	
Schadde <i>et al.</i> , 2014 (66)	Prospective cohort study	202	80 (RH)	98	40	9 (90 days)	Age <60, CRLM group with better survival
Sandstrom <i>et al.</i> , 2018 (67)	Randomized controlled trial	48	68 (RH)	92	43	9 (90 days)	

ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; FLR, future liver remnant; RH, relative hypertrophy; CRLM, colorectal liver metastasis.

improve outcomes. These alternatives usually employ a different method for the initial hepatic transection, for example through tourniquet application or radiofrequency ablation, but thus far their success remains unproven (66,74,77-81). Lengthening the interval between stage 1 and 2 to allow time for FLR maturation has also been suggested, but at least partially mitigates against the benefits provided by the increased KGR (71).

Given the associated morbidity and mortality of the technique, ALPPS is currently reserved for situations in

which the risk-benefit ratio justifies its potential dangers (82,83).

### Combination treatment of the portal vein and hepatic artery

Although PVE reliably produces FLR hypertrophy in patients with otherwise healthy livers, the response is more variable in those with underlying liver disease. This prompted efforts to further augment FLR hypertrophy,

with one approach focusing on added hepatic artery embolization (transarterial embolization, or TAE). Because the degree of FLR hypertrophy correlates directly with the extent of ischemia (84), it has been postulated that increasing ischemic severity via addition of TAE would produce more rapid and extensive FLR growth. This effect is likely to be further augmented via both obliteration of intrahepatic arterioportal shunts, which are common in diseased and tumor-bearing livers, and elimination of compensatory increases in arterial inflow, which can occur after PVE and is termed the hepatic arterial buffer response (85,86). Additionally, TAE provides a strong anti-tumor effect, which may help to counteract the stimulatory effect on tumor growth observed following PVE and help to limit tumor progression in the interval between embolization and resection (9,86-93). The main theoretical limitation to this technique is the potential for ischemic necrosis of the noncancerous hepatic parenchyma, which has led to the adoption of an interval of days to weeks between performance of the two procedures (84,90,91).

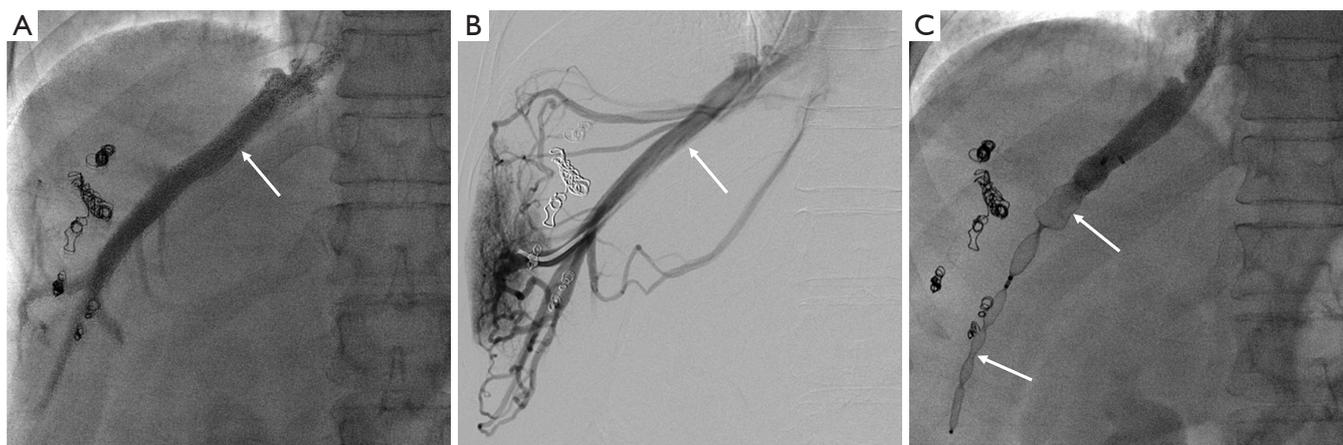
Sequential TAE+PVE has been evaluated in numerous small studies using variable order of and intervals between the two treatments. The most common approach utilizes TAE followed by PVE, although Gruttadauria *et al.* performed PVE first, reserving TAE for patients in whom sufficient hypertrophy was not initially achieved (85,94). This latter approach has the appeal of potentially sparing patients who achieve sufficient post-PVE hypertrophy the need for a second intervention with its associated risks and surgical delay. Most series suggest that combination therapy does produce a more pronounced effect on FLR hypertrophy when compared with isolated PVE (39,84,86,91,94-96). For example, Ogata *et al.* and Vilgrain *et al.* both independently reported a 12% increase in FLR size for TAE+PVE compared with 8% for isolated PVE (although only the former reported a P value, which confirmed statistical significance at  $P=0.022$ ) (91,96), while Yoo *et al.* reported increases of 7.3% and 5.8% for TAE+PVE and isolated PVE ( $P=0.035$ ), respectively (95). In a series of 7 patients, Gruttadauria *et al.* described mean hypertrophy of 14.75% after initial PVE which then increased to 46.8% following TAE 6 weeks later (P value not reported), although most patients in this series were without underlying liver disease (94). This greater degree of hypertrophy translated to positive post-operative outcomes, with Ogata *et al.*, Vilgrain *et al.*, and Yoo *et al.* all reporting significantly increased disease-free survival following TAE + PVE, and the latter further reported significantly increased

overall survival, findings which the authors attributed to reduced early recurrence resulting from increased tumor necrosis and decreased dissemination (91,95). Of note, in the largest and only multicenter series available, Peng *et al.* found no significant difference in rates of FLR hypertrophy between PVE and TAE + PVE (97). However, the authors concluded that the procedure is safe and effective for simultaneous induction of FLR hypertrophy and treatment of intrahepatic disease while awaiting resection.

Initial concerns regarding hepatic parenchymal necrosis were ultimately not borne out. Although treatment is generally accompanied by a prominent transaminitis with the peak dependent in part upon the interval between the two interventions, levels typically normalize by the time of surgery without clinical consequence (39,84,90,91,95,96,98). Pathologic evaluation of resection specimens has shown overall minimal necrosis of the noncancerous parenchyma, in contrast to the substantial tumor necrosis which occurs (84,86,90). In fact, the differential effect on tumor-bearing liver has prompted several authors to propose that combination TAE + PVE may be sufficient therapy in its own right if inadequate hypertrophy precludes resection (89,91,96). Additionally, it has been shown that should resection not be performed, it is safe to perform post-PVE TAE (99,100). Of note, several cases of hepatic abscess formation and/or sepsis were reported in patients who had undergone prior biliary intervention, suggesting particular care should be taken when evaluating these patients for TAE + PVE (94,98,101).

### LVD

A modification to the TAE+PVE technique, spurred by initial concerns regarding excessive hepatic ischemia and consequent infectious complications, involves embolization of the portal and hepatic veins, termed LVD (102) (Figure 5). In theory, this technique induces a degree of hepatic ischemia intermediate to PVE and TAE + PVE. By occluding hepatic venous outflow, any residual portal vein inflow is further reduced and hepatic artery inflow, while not eliminated, is decreased, helping to mitigate the hepatic arterial buffer response. Embolization of the right hepatic vein (RHV), for example, produces outflow obstruction in the right posterior and, to a lesser extent, anterior segments, ultimately affecting two-thirds of the right hepatic lobe volume (102,103). An auxiliary benefit of this technique is the potential for pre-operative stimulation of venous collateral development (104). Because hepatic congestion



**Figure 5** A 66-year-old woman with metastatic breast cancer, planned for right hepatectomy and referred for pre-operative portal vein embolization (PVE) due to small projected future liver remnant (FLR). Patient underwent prior PVE embolization with inadequate hypertrophy of the FLR, so embolization of the hepatic vein was undertaken. Angiogram (A) and DSA (B) showing the pre-embolization appearance of the right hepatic vein (arrow). (C) After embolization with multiple Amplatzer plugs, flow within the right hepatic vein is occluded (arrow).

resulting from outflow impairment has been shown to limit hepatic regeneration, the stimulation of venous collateral development before surgery may help to limit post-operative congestion that might otherwise contribute to graft failure (104-106).

Although initially reported as a sequential technique in which PVE was performed first followed by HVE several weeks later (101,102), concurrent PVE and HVE has been shown to be feasible, safe, and effective (12). Likewise, while early reports used a transvenous approach, Guiu *et al.* described a trans-hepatic approach which they favored for its ease of performance and ability to embolize immediately-developing veno-venous collaterals (12) (Figure 5B). In brief, the procedure is performed by advancing two sheathes into the liver via a transhepatic approach, one into the target hepatic vein and the other into a right portal vein branch. PVE is performed in standard fashion, while HVE is performed by first placing a vascular plug in the proximal hepatic vein to prevent migration of embolization material and then injecting a 1:1 mixture of lipiodol:n-butyl-cyanoacrylate upstream (12). The middle hepatic vein (MHV) can be embolized in addition to the RHV, which is termed extended liver venous deprivation (eLVD) (107). Of note, initial attempts by Hwang *et al.* to place an IVC filter and embolize with coils were complicated by migration of both, so the approach was abandoned (101,102).

Although preliminary, initial results have thus far been promising (12,101,102,108). In 12 patients who underwent

sequential PVE and RHV embolization, Hwang *et al.* reported an increase in FLR from 34.8% before PVE to 39.7% 1–2 weeks after PVE to 44.2% 2 weeks after HVE (102). Similarly, following concurrent PVE and HVE, Guiu *et al.* reported an increase from 28.2% to 40.9%, although the series of 7 patients did not include any with cirrhosis or a control group who underwent isolated PVE (12). In a subsequent study directly comparing PVE and LVD in 12 patients with Klatskin tumor, FLR hypertrophy (using standardized FLR ratio) was significantly greater following LVD than PVE (58% *vs.* 37%, respectively;  $P=0.017$ ), and there was a trend towards shorter median postoperative hospital stay and 90-day mortality (109).

For eLVD, which involves embolization of the entire right hepatic venous outflow, results appear even more dramatic: FLR volume increased from 20.8% to 33.4% (standardized FLR ratio), KGR was 25 cc/day compared to 4.4 cc/day after PVE and 9.3 cc/day after LVD, and FLR function increased by 64.3% (107). Although transaminases peaked and then returned to baseline in a manner analogous to TAE + PVE, no complications related to hepatic necrosis occurred (12,101,102,107). Although ALPPS produces comparable FLR hypertrophy to eLVD, the functional increase as measured by  $^{99m}\text{Tc}$ -mebrofenin hepatobiliary scintigraphy is substantially less (65.7% for eLVD *vs.* 28.2% for ALPPS), potentially explaining the high morbidity and mortality that accompanies the surgical procedure (110,111).

## RL

RL is yet another alternative to PVE and its myriad variants for inducing FLR hypertrophy. The potential utility of this technique was first appreciated during analysis of the effects of radioembolization on the liver, where lobar treatment was noted to produce atrophy of the ipsilateral lobe and hypertrophy of the contralateral lobe (13,112-114). Principally, the technique is very similar to standard transarterial radioembolization in which yttrium-90 ( $^{90}\text{Y}$ ) labeled microspheres are administered into the arteries supplying the tumor-bearing liver. However, it differs from the standard therapeutic approach in necessitating more proximal administration from a lobar artery as opposed to a segmental or subsegmental vessel, as well as utilization of higher overall radiation dose (115). This results in treatment not just of the tumor itself but of the ipsilateral non-tumorous hepatic parenchyma as well. Microvascular ischemia and high-dose brachytherapy result in hepatocyte injury and death, acting as locoregional treatment of the hepatic malignancy with simultaneous induction of FLR hypertrophy. Because of this, RL can be utilized either as a primary treatment in its own right or as a bridge to surgical resection (115). Although it shares the advantage of added tumor treatment with TAE + PVE, RL provides the benefit of being purely trans-arterial in nature without a transhepatic or portal venous component, thus allowing for single session treatment and facilitating intervention in the presence of portal vein thrombosis. In fact, portal vein thrombosis has been shown to be associated with increased degrees of FLR hypertrophy following RL, possibly as a result of functioning as a “natural PVE” (116).

Although most series report the effectiveness of RL for both tumor treatment and induction of FLR hypertrophy, only the latter is discussed here to place it in the context of as other regenerative modalities. Since its initial description in 2009, multiple series have demonstrated its efficacy albeit with wide variance in administered dosage, method of delivery (glass versus resin microspheres), number of sessions, treated pathology, underlying liver function, outcome assessment, and length of follow-up (Table 3). In 2014, Teo *et al.* performed a systematic review of these series (117) which included seven studies comprising 312 patients, of which the majority had HCC (69%) and underwent treatment of the right lobe (91%) (116,118-123). After noting the aforementioned data heterogeneity, the authors reported that the overall degree of FLR hypertrophy ranged between 26% and 47% at 44 days to 9 months. Included

within this review was a direct comparison between RL and PVE, which found a significantly greater degree of hypertrophy with PVE (PVE 61.5%, RL 29.0%) within a shorter median time frame (PVE 33 days, RL 46 days) (122). Additionally, Vouche *et al.* and Fernandez-Ros *et al.* concluded that the post-embolization KGR is slower than that achieved with other therapies (116,121). Consequently, evaluation of the extent of hypertrophic response should not occur before 3 months post embolization and, if not sufficient at that time, again at the 6-month timepoint (124).

Although there have been multiple attempts to identify factors associated with the degree of post-embolization hypertrophy, findings thus far have been inconsistent. Vouche *et al.*, for example, identified the presence of portal vein thrombosis as the only predictor of increased FLR, whereas Goebel *et al.* found younger patient age, absence of portal hypertension (normal spleen size, platelet count  $\geq 100/\text{nL}$ , absence of ascites), absence of advanced liver disease (low Child Pugh score), and low tumor burden to each be independently associated with increased KGR (116,125). Teo *et al.* described substantially greater hypertrophy in patients with underlying hepatitis B versus those with hepatitis C or alcoholic cirrhosis (44.5% *vs.* 7.7% respectively;  $P=0.050$ ), a finding which the authors attributed to the health of the liver parenchyma (123). Palard *et al.* found that a mean hypertrophy rate of  $>10\%$  was associated with a dose to the healthy liver parenchyma of  $\geq 88$  Gy, and/or to tumor of  $\geq 205$  Gy when tumor volume is  $\geq 100$  cm<sup>3</sup> (124).

RL is in general well-tolerated, with adverse events common to those seen in standard radioembolization (pain, flu-like symptoms, nontarget embolization) and typically transient, easily managed, or avoidable with good technique (116). Multiple studies have reported post-embolization imaging findings suggestive of developing portal hypertension without clinical consequence (112,121,123), and Vouche *et al.* described transient worsening of Child-Pugh scores which subsequently returned to baseline (116). Although surgical resection is performed much less commonly following RL than after other hypertrophic techniques secondary to use as destination therapy, preliminary reporting of surgical outcomes is promising. In a series of 13 patients undergoing RL followed by resection, Lewandowski *et al.* reported low post-operative morbidity, no mortality, and only one case of liver insufficiency, the latter secondary to a primary sclerosing cholangitis flare; after a median follow-up of 604 days, only one death had occurred (126). A subsequent

**Table 3** Summary of pertinent series on radiation lobectomy

Author	Date	Patients	Tumor types	Embolization agent	Treated lobe	Dose	# Treatment sessions	Follow-up	Degree hypertrophy
Jakobs (overlap w/Vouche)	2008	10	Mixed metastases	Glass	Right	120 Gy (mean)	1	139 days (mean)	20.3% (mean), 17.2% (median)
Gaba (overlap w/Vouche)	2009	20	HCC [17], CCA [3]	Glass	Right	175 Gy (mean), 132 Gy (median)	1.7	18 months (mean)	40% (mean)
Ahmadzadehfar*	2013	24	Mixed metastases	Resin	Right	N/A [activity 1.67 GBq (mean), 1.75 GBq (median)]	1	44 days (mean), 36 days (median)	47% (mean), 34% (median)
Edeline*	2013	34	HCC	30 glass, 4 resin	23 right, 11 left	122 Gy (median)	1	3 months	38% (mean)
Vouche*	2013	83	HCC [67], CCA [8], mCRC [8]	Glass	Right	112 Gy (median)	1	>9 months	45% (median)
Theysohn* (overlap w/Goebel)	2013	45	HCC	Glass	Right	112 Gy (mean)	1	12 months	40.1% (mean)
Fernandez-Ros*	2014	83	HCC [52], CCA [4], mCRC [13], 14 [other]	Resin	66 right, 17 left	N/A	1	>26 weeks	45% (mean)
Garlipp*	2013	26	Mixed metastases	Resin	Right	N/A [activity 1.2 GBq (mean)]	1	46 days	29% (mean), 25.3% (median)
Teo*	2014	17	HCC	Resin	Right	N/A	1	5 months (median)	34.2% (mean)
Lewandowski (overlap w/Vouche)	2016	13	HCC [10], CCA [2], mCRC [1]	Glass	Right	154 Gy (median)	1.4	40 days (median)	30% (median)
Goebel	2017	75	HCC	Glass	Right	113 Gy (mean)	1	6 months	38.9% (mean)
Palard	2017	73	HCC	Glass	Right	149.9 Gy (mean)	1	5.9 months (mean)	35.4% (mean)
Gabr (overlap w/Vouche)	2018	20	HCC	Glass	Right	128 Gy (median)	1.2	Not reported	23.3% (median)

\*, studies included in the systematic review by Teo *et al.* HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; mCRC, metastatic colorectal cancer.

study from the same group which included 20 patients who underwent RL and 11 who underwent radiation segmentectomy was similarly promising (127).

## Conclusions

PVE remains a proven, highly effective technique for induction of liver hypertrophy prior to operative intervention in patients who would otherwise not be surgical candidates, but is not universally effective.

Attempts to iterate on and improve the technique, although promising, remain unproven and, in some cases, may place patients at higher risk of adverse outcomes. Furthermore, stimulation of tumor growth following PVE remains a poorly understood but potentially catastrophic concern (63,128-130). Inconsistencies in patient selection, technical approach, reporting standards, and outcome measures have severely limited comparisons between these techniques and leave the inexperienced interventionalist with many choices and no clear path forward. Direct comparative

studies with histopathologic correlation will be needed for further elucidate the mechanisms underlying and outcomes produced by these techniques, and to be able to better offer patients a safe, effective, and individualized approach to hepatic regeneration.

## Acknowledgments

*Funding:* None.

## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn.2019.09.10/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Cite this article as:** Kim D, Cornman-Homonoff J, Madoff DC. Preparing for liver surgery with “Alphabet Soup”: PVE, ALPPS, TAE-PVE, LVD and RL. *HepatoBiliary Surg Nutr* 2020;9(2):136-151. doi: 10.21037/hbsn.2019.09.10