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

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Abstract: Future liver remnant (FLR) 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

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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 20th 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
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). Intestinally-derived trophic factors such as epidermal growth factor (EGF) are delivered to the injured liver 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 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 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 (TELV) is calculated using the following formula: 

$$\text{TELV} = -794.41 + 126.28 \times \text{BSA}$$

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).

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 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) (Figure 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,
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 periporal 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 metanalyses, mean FLR hypertrophy rates were reported to be 37.9–49.4% and 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,
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
Schinitzbauer 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

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

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

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

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

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 arteriportal 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
resulting from outflow impairment has been shown to limit hepatic regeneration, the stimulation of venous collateral development before surgery may help to limit postoperative 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 99mTc-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 (90Y) 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 transthepatic 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 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 ≥100/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 ≥88 Gy, and/or to tumor of ≥205 Gy when tumor volume is ≥100 cm³ (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

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

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

A 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.

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None.

Footnote

Conflicts of Interest: 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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