REVIEW

For reprint orders, please contact: reprints@futuremedicine.com

Controversies of preoperative portal vein embolization

Hepatic Oncology

Benjamin J May¹ & David C Madoff^{*1}

Practice points

- Portal vein embolization (PVE) is an image-guided procedure that reduces postoperative morbidity of major hepatic resection by inducing hypertrophy of the future liver remnant (FLR).
- A variety of embolic agents have been described with technical success. The two most commonly described are *n*-butyl cyanoacrylate liquid embolic and size-calibrated microparticles.
- *n*-butyl cyanoacrylate is typically faster to administer, requires less iodinated contrast and may induce a more robust FLR hypertrophy. Most operators find microparticles easier to control and safer to administer to segment 4. Clinical outcomes and resection rates are similar.
- Prior to extended right hepatectomy, some authors argue that PVE should include segment 4 citing data that FLR hypertrophy is improved. Redirecting portal flow to this tumor-bearing segment is another concern. Others prefer not to embolize segment 4 out of concern for nontarget embolization. In the larger series describing segment 4 embolization, microparticles are typically used and nontarget embolization rates are very low.
- Continuing chemotherapy between PVE and resection has been debated. Earlier data that suggested chemotherapy limits FLR hypertrophy has not been supported by subsequent larger series. Current data support the use of chemotherapy between PVE and resection, particularly for colorectal metastases.
- Transarterial radiation lobectomy results in contralateral liver hypertrophy but at rates much slower than PVE. This technique is, therefore, a poor substitute for PVE but may be of value in select cases where borderline resectable disease is ultimately downsized with transarterial therapy.
- Surgical alternatives to PVE include portal vein ligation (PVL) and the more extensively associated liver partition and portal vein ligation.
- A meta-analysis comparing PVL to PVE found a trend for slower rates of FLR hypertrophy for PVL that approached but did not meet statistical significance. PVL is more invasive than PVE but is sometimes performed in combination with other planned abdominal surgery.
- The associated liver partition and portal vein ligation procedure, first described in 2012, results in very fast FLR hypertrophy and facilitates earlier resection compared with PVE. A meta-analysis, however, showed a mortality rate of 11% and serious morbidity rate of 44%. Refinements in technique may be able to achieve improved safety of the procedure. It remains unclear whether shortening resection by several weeks truly prevents disease progression.

¹Department of Radiology, Division of Interventional Radiology, New York-Presbyterian Hospital/Weill Cornell Medical Center, New York, NY, USA

^{*}Author for correspondence: Tel.: +1 212 746 2602; Fax: +1 212 746 8891; dcm9006@med.cornell.edu

Portal vein embolization (PVE) is a safe, percutaneous procedure that has been proven to lower the complication rates of curative intent large-volume hepatic resection by inducing hypertrophy of the future liver remnant. While the safety and efficacy of PVE has been well substantiated, there remains controversy with regards to the technical details, periprocedural management, and whether alternative methods of achieving future liver remnant hypertrophy are preferable to PVE. This paper will address those controversies and offer recommendations based on available data.

First draft submitted: 13 November 2015; Accepted for publication: 14 January 2016;
Published online: 29 March 2016

KEYWORDS

• associated liver partition
• controversies • liver
volumetry • portal vein
embolization • portal
vein ligation • two-stage
hepatectomy

The incidence of primary liver cancer in the USA has increased steadily over the past decade while the liver remains a common organ for metastatic disease [1]. Surgical resection plays a central role in the management of primary liver tumors, as well as metastases confined to the liver. Because the liver is capable of regeneration, a majority of the organ can be resected, if needed. However, major hepatic resection can be complicated by sequelae of liver insufficiency, particularly in the perioperative period, when liver regeneration is initiating. The percentage of liver that remains after resection, termed the future liver remnant (FLR), has been identified as a strong, independent predictor of perioperative complications [2,3].

Portal vein embolization (PVE) is an image-guided procedure used to induce hypertrophy of the FLR prior to planned hepatic resection. In this procedure, portal blood flow is redirected from the tumor-bearing liver segments to the FLR resulting in atrophy of the tumor-bearing segments and hypertrophy of the FLR. PVE has been proven to reduce rates of postoperative liver insufficiency, as well as enable curative intent surgery, in patients who would have otherwise not been surgical candidates [4,5].

Complication rates are exceedingly low. In one meta-analysis pooling data from 37 studies with a total of 1008 subjects, the overall complication rate was 2.2% and 0% mortality [6]. Distefano *et al.* characterized the 12 complications (6.4%) occurring in 188 patients undergoing PVE [7]. These included complete portal vein thrombus (n = 1), migration of embolic material to the FLR requiring angioplasty (n = 2), hemoperitoneum (n = 1), rupture of a metastasis into the gallbladder (n = 1), transient hemobilia (n = 1) and transient liver failure (n = 6). There was no procedure-related mortality and only the complete portal thrombosis precluded subsequent surgery. Owing to its established safety and efficacy, PVE has

been accepted worldwide as an adjunct to major hepatic resection [8].

Nonetheless, controversy exists with regards to procedural details, periprocedural management, and whether alternative methods of inducing FLR hypertrophy are preferable. This paper will address the following controversial topics with respect to PVE: How should preoperative liver volumetric assessment be performed? What is the best embolic agent for PVE? Should PVE include segment 4 prior to extended right hepatectomy? Which percutaneous approach is preferred, contralateral or ipsilateral? Should chemotherapy be continued in the period between PVE and resection? Is radiation lobectomy a reasonable alternative to PVE? Is surgical portal vein ligation (PVL) or associated liver partition and PVL (ALPPS) preferable to PVE? Hopefully, this article will adequately address these controversies and allow the reader to gain a clearer understanding of the most current appropriate utilization of preoperative PVE.

Background

A brief summary of the pathophysiology and technique of PVE will provide a background for examining the controversial topics outlined above. Following embolization or surgical resection, changes in hemodynamics and signaling pathways lead to hypertrophy of noninjured hepatic segments. The portal vein plays an important role in transporting trophic signaling molecules to the noninjured liver segments [9,10]. The rate of hypertrophy after surgical resection is greater than after PVE, likely owing to the more robust inflammatory response.

Although initially described as an open surgical technique, PVE is now commonly performed as a percutaneous procedure, often on an outpatient basis [11]. Using image guidance, a portal venous branch is punctured percutaneously and a catheter advanced within the portal tree. Embolic material is administered to

tumor-bearing segments diverting portal blood, rich in trophic factors, to the FLR. This results in apoptosis and atrophy of the embolized segments and hypertrophy of the FLR. Liver regeneration begins within a few hours on a cellular level and measurable changes in liver volume are typically achieved within a few weeks [12,13]. However, patients with underlying liver damage or cirrhosis may demonstrate attenuated rates of hypertrophy [14].

The decision to employ PVE prior to hepatic resection is made on a patient-by-patient basis taking into consideration a variety of factors including patient age and comorbidities, complexity of the surgery and regional practice patterns. Although no strict cutoffs exist, there are data to support the use of PVE in otherwise normally functioning livers when FLR is less than 20% of total liver volume (TLV) [4]. This recommendation is supported by Kishi *et al.* who analyzed the outcomes of 301 consecutive patients who underwent extended right hepatectomy. This group found that patients with preoperative FLR less than 20% of TLV had significantly higher rates of postoperative liver insufficiency and death. Patients who increased their FLR to greater than 20% of TLV had similar outcomes as patients with greater than 20% at baseline. Based on this and other supporting data, a Consensus Conference on the Multidisciplinary Treatment of Hepatocellular Cancer in 2010 recommended PVE for patients with an FLR less than 20% and otherwise normal liver function [15]. Some groups use lower threshold for employing PVE, in the range of FLR less than 30% of TLV, with otherwise normal liver function. Differences in way in which liver volumetric assessment is performed may explain this discrepancy, as will be addressed later in this article.

In patients with compromised liver function as evidenced by hepatosteatosis, hepatotoxic chemotherapy exposure or compensated cirrhosis, PVE is often employed when %FLR is less than 30–40% of TLV [16–18]. Because the right liver segments compose a majority of liver volume, PVE is typically only indicated prior to right hepatectomy (segments 5–8) or extended right hepatectomy (right hepatectomy + segment 4).

In addition to traditional hepatic resection, PVE has also been incorporated in a multistage approach to treating bilobar hepatic metastases, termed two-stage hepatectomy [5]. This strategy

has enabled patients with bilobar metastases, once considered unresectable disease, to undergo curative intent surgery. In the first stage procedure, metastases in the FLR are resected or ablated. Next, PVE is performed to induce necessary hypertrophy of the FLR. Finally, a large volume partial hepatectomy is performed. In some cases, PVL is performed during the first stage surgery as an alternative to PVE, as will be discussed later in this article.

How should preoperative liver volumetric assessment be performed?

PVE is indicated when the FLR volume is considered high risk for developing perioperative liver insufficiency. The absolute FLR volume alone, however, is inadequate for predicting a risk of liver insufficiency because larger patients require larger liver volumes to support function. Therefore, a standardized FLR, expressed as the percentage of FLR with respect to total functioning liver volume (%FLR), is used in the assessment of patients for PVE.

In order to calculate a standardized FLR, volumes of FLR and total functioning liver must be obtained. The FLR volume is typically measured directly using cross-sectional volumetric software. A direct measurement of the total liver volume is possible as well but requires subtracting the tumor volume or other nonfunctional lesions from surrounding functional liver. This direct measurement of tumor volume can be imprecise in cases where infiltrative tumor borders are indistinct. The method is also tedious in cases where multiple tumors are required to be measured.

Alternatively, total estimated liver volume (TELV) can be calculated based on the predictive relationship between body size and functioning liver volume. Vauthey *et al.* derived the following formula for TELV by analyzing liver volume and body surface area (BSA) in 292 western adults, measured at major medical centers in the USA and Europe [19].

$$\text{TELV} = -794.41 + 1267.28 \times \text{BSA}$$

Although many similar models have been described in the literature, this formula was found to be most accurate for adults in a meta-analysis comparing 13 published models for estimating liver volume [20]. Additionally, Shah *et al.* found percent FLR based on the TELV formula above predicted postoperative liver failure better

than percent FLR based on direct cross-sectional measurement of total liver volume or using the ratio of FLR to bodyweight [21].

• Summary & recommendations

When evaluating patients for PVE, the percent FLR with respect to total liver volume should be used rather than absolute FLR volume in order to account for differences in patient size and therefore their liver function requirements. If an estimated total liver volume is to be used, data support the use of the formula described by Vauthey *et al.* ($TEL\text{V} = -794.41 + 1267.28 \times \text{BSA}$). For centers initiating a PVE program, we would recommend adopting the TELV method of calculating total liver volume due to its ease of use, reproducibility and ability to compare values to the extensive outcomes literature that has been published based on this method of calculating TELV. For centers with practice patterns based on direct volumetric measurements, using published threshold values based on the TELV formula may not hold true.

What is the best embolic agent for PVE?

As the utilization of PVE has increased steadily in the past few decades, so has the list of embolic agents that have been used to achieve PVE. Table 1 provides a description of various embolic agents that have been reported, as well as technical factors influencing their use. The

ideal embolic agent should achieve reliable vessel occlusion/FLR hypertrophy, be well tolerated, cost effective and easily administered. While a detailed analysis of each type of agent is beyond the scope of this article, a broader comparison of particulate embolics and liquid embolics will shed light on the advantages and disadvantages of each.

Particulate embolics are commonly employed for PVE as interventional radiologists tend to be familiar with their administration as they are commonly used for other embolotherapy procedures. With adherence to sound administration technique, nontarget embolization is rare and can be quickly identified before nontarget branches are occluded. This is particularly critical when embolizing segment 4 due to its close proximity to the FLR (segments 2 and 3). However, the volume of particles required to occlude the portal venous branches is relatively high and can add to the cost, time and contrast dose to the procedure.

Size-calibrated spherical particles are less likely to clump when compared with nonspherical polyvinyl alcohol (PVA) particles and are, therefore, able to achieve more distal microvascular embolization. Madoff *et al.* compared FLR hypertrophy in patients treated with either PVA particles (355–1000 μm; n = 23) and coils or tris-acryl gelatin microspheres (100–700 μm; n = 21) and coils [22]. This study found that PVE

Table 1. Various embolic agents reported.		
Agent	Embolic category	Comments
Gelatin sponge	Temporary embolic, typically administered as small fragments suspended in slurry	Agent used in initial PVE description, its use in PVE has largely been abandoned due to cases of early recanalization and inadequate FLR hypertrophy
PVA	Nonspherical particle	Known to clump and therefore functionally behaves as a larger particle than the size description implies
Tris-acryl microspheres	Size-calibrated spherical particles	Available in various sizes, less prone to clump due to hydrophilic coating and, therefore, smaller particles achieve more distal embolization
Ethanol	Liquid embolic	Induces necrosis of the vascular endothelium resulting in inflammation and relatively high rates of FLR hypertrophy. Risk of nontarget embolization thought to be higher due to flow dynamics. Intense inflammation induced causes significant pain and may be detrimental in patients who do not ultimately proceed to resection
n-butyl cyanoarylate	Liquid embolic	Medical glue, US FDA approved for cerebral arteriovenous malformations. Polymerizes rapidly making nontarget embolization particularly concerning
Fibrin glue	Liquid embolic	High rates of recanalization. Requires multilumen balloon catheters for administration. Utilized primarily in Asian countries
Sodium tetradecyl sulfate	Foam sclerosant	Agent used primarily for peripheral venous sclerosing. Requires balloon occlusion catheters to prevent nontarget embolization

FLR: Future liver remnant; PVA: Polyvinyl alcohol; PVE: Portal vein embolization.

with the smaller tris-acryl gelatin microspheres resulted in significantly greater FLR volume hypertrophy ($p = 0.0011$) and resection rates ($p = 0.02$).

Liquid embolic agents, such as *n*-butyl cyanoacrylate (NBCA) and ethanol have also been described with technical success [23,24]. These agents result in greater inflammatory process and robust FLR growth, which may be particularly advantageous in scenarios where FLR hypertrophy may be compromised, such as cirrhosis. Liquid embolics tend to be administered over a shorter time frame than particle embolics and can result in faster procedures. The contralateral approach has been recommended for NBCA administration due to rapid polymerization and concern for catheter manipulation within embolized segments. With NBCA, the user must be very familiar with the delivery system as the polymerization process is rapid and nontarget embolization can very quickly occlude FLR branches.

Bent *et al.* described the use of a nitinol plug in combination with histoacryl glue as a means of preventing nontarget embolization [25]. Sixteen patients underwent PVE from an ipsilateral approach. The nitinol plug was deployed in the right portal vein near its origin and then distal embolization was performed with the histoacryl glue. There were no cases of nontarget embolization during the procedure or on follow-up imaging. Interestingly, before their use of the nitinol plug, the authors reported a 30% incidence of nontarget embolization (three of ten patients) when using histoacryl glue and lipiodol mixture, two of which resulted in inadequate FLR hypertrophy.

Head-to-head comparisons of NBCA and microparticles are limited to animal studies or single-center retrospective analysis. In a pig study, de Baere *et al.* evaluated the histologic liver changes that occurred 7 days after PVE performed with four different embolics (NBCA, hydrophilic gel, PVA) 50–150 μm and PVA 700–900 μm on 20 pigs, five per group [26]. The NBCA group showed greater size of hepatic lobules within the nonembolized segments compared with the other embolic agents ($p = 0.01$). Fibrosis in the embolized liver was greater in the NBCA and 50–150 μm PVA groups compared with the other two ($p = 0.002$). Cross-sectional volumetric data were not collected.

Similarly, Tsoumakidou *et al.* compared NBCA to sodium acrylate-vinyl alcohol

copolymer particles (50–100 and 100–150 μm) in a pig model, six pigs per group [27]. Embolization was performed to stasis and liver volumes were assessed by CT at 14 and 28 days. There was one incidence of nontarget embolization in the NBCA group though blood flow to this segment remained patent. The NBCA group demonstrated higher FLR hypertrophy at both 14 and 28 days compared with the sodium acrylate-vinyl alcohol copolymer particles (52 and 66% vs 12 and 10%; $p < 0.05$).

Guiu *et al.* retrospectively analyzed a group of 34 patients who underwent PVE over a 2-year period with NBCA used in 20 consecutive patients during the first year and 14 consecutive patients treated with microparticles (100–300 μm) the following year [28]. PVE was technically successful in each case. There was one case of nontarget embolization within the NBCA group noted incidentally on 1-month follow-up CT. The NBCA group demonstrated a greater increase in FLR volume following PVE compared with the microparticle group ($+74 \pm 69\%$ vs $+23 \pm 14\%$, respectively; $p < 0.05$). The microparticle group required a higher volume of contrast compared to the NBCA group ($p < 0.01$). There was no difference in the percentage of patients who went on to resection (75% NBCA vs 78.6% microparticle). It is worthwhile to note that at the time of the study, there was potential for operator bias since the authors had extensive experience with NBCA but only limited experience performing PVE with microparticles and coils.

• Summary & recommendations

There are currently no prospective randomized human trials comparing the various embolic agents. The available data, though limited, suggest that NBCA may lead to a greater degree of FLR hypertrophy as explained by an increase in periportal fibrosis. NBCA can typically be administered in a shorter amount of time and with less iodinated contrast compared with microparticles. There are no data to suggest that any embolic agent results in improved resection rates or clinical outcome.

In practice, the decision to employ one agent over the other is often made based on operator experience, the cost and availability of the specific agents and the associated specialty catheters that may be needed for delivery. When particle embolization is employed, size-calibrated microspheres are recommended in order to achieve

distal microvascular embolization. Additionally, if segment 4 is to be treated, the authors recommend particles as users typically find it easier to detect and prevent nontarget embolization.

Should PVE include segment 4 prior to extended right hepatectomy?

Extended right hepatectomy is the surgical resection of the right liver plus segment 4 leaving only the left lateral bisegment. The decision to include segment 4 with right PVE (RPVE + 4) prior to extended right hepatectomy remains controversial. Proponents of RPVE + 4 argue that without embolization of segment 4, portal flow will be directed to this tumor-bearing segment and place the patient at increased risk for disease progression prior to hepatectomy. In addition, they cite data that shows improved hypertrophy of segments 2 and 3 [29]. However, extending PVE to include segment 4 is more technically demanding [30]. Authors who prefer not to include segment 4 argue that adequate hypertrophy can still be achieved with right PVE only [31]. Additionally, they argue that the branches to segments 2 and 3 often arise in close proximity to segment 4 and are, therefore, at increased risk for nontarget embolization of the FLR.

To address this concern, Kishi *et al.* compared FLR hypertrophy in 58 patients who underwent rPVE + 4 with 15 patients who underwent RPVE only [32]. After a median of 27 days, the segment 2 + 3 volume increase was greater for RPVE + 4 compared with rPVE (median, 106 vs 141 ml; $p = 0.044$). Additionally, the hypertrophy rate was higher for RPVE + 4 compared with RPVE (median, 54 vs 26%; $p = 0.021$). On the other hand, de Baere *et al.* compared outcomes of 70 patients who underwent RPVE with 37 patients who underwent RPVE + 4 [33]. The RPVE group increased %FLR of TLV from $25 \pm 8\%$ to $39 \pm 9\%$. The RPVE + 4 group increased %FLR from $22 \pm 8\%$ to $35 \pm 10\%$. There was no significant difference between the two groups.

Although nontarget embolization is a concern when embolizing segment 4, large series, however, have failed to demonstrate an increased complication rate for RPVE + 4 compared to RPVE alone. In the Kishi *et al.* publication described above, complication rates were similar between the RPVE + 4 and RPVE groups (10 vs 7%, respectively; $p > 99\%$) and no complications precluded subsequent resection [32].

Ribero *et al.* reported on complication rates of 86 patients who underwent RPVE + 4 compared to 24 patients who underwent RPVE [3]. Nontarget embolization to the FLR occurred in one patient (1%) in the RPVE + 4 group. The overall complication rates were similar between the two groups (RPVE: 4% vs RPVE + 4: 8%, $p = 0.417$).

In 2013, Shindo *et al.* reported on the outcomes of 144 patients who underwent intended RPVE + 4 [34]. The overall technical success rate was 96.5% (139 of 144). In three patients (2%), RPVE + 4 was suspended due to decreases in portal venous flow during the procedure. In two patients (1.4%), portal flow abnormalities post-procedure resulted in inadequate FLR hypertrophy. The authors reported adequate regeneration of the FLR in 139 (98.5%) with FLR volume to bodyweight ratio increasing from 0.33 to 0.52% ($p < 0.0001$).

Most recently, Mise *et al.* studied regeneration of segments 2 and 3 after PVE in patients undergoing two-stage hepatectomy [29]. This study compared hypertrophy of segments 2 and 3 in 44 patients who underwent PVE as part of a two-stage hepatectomy to 116 patients who underwent PVE prior to right hepatectomy. The study found attenuated rates of segments 2 and 3 hypertrophy for two-stage hepatectomy compared with right hepatectomy alone. On multivariate analysis, extending PVE to include segment 4 was found to be an independent predictor of higher degree of hypertrophy ($p < 0.01$; 95% CI: 1.61–3.71) and higher kinetic growth rates ($p < 0.01$; 95% CI: 1.64–3.78). The authors concluded that PVE should include segment 4 as part of two-stage hepatectomy when the second stage resection requires extended right hepatectomy.

• Summary & recommendations

Although earlier studies showed similar rates of hypertrophy for RPVE compared with RPVE + 4, larger subsequent series have supported improved rates of hypertrophy when embolization is extended to segment 4. The concern for nontarget embolization of FLR is valid but its incidence is reported on the order of 1–2% in experienced hands. When technically feasible, data support the inclusion of segment 4 during PVE prior to extended right hepatectomy, particularly in the setting of two-stage hepatectomy or other scenarios when FLR hypertrophy may be compromised.

Which percutaneous approach is preferred, contralateral or ipsilateral?

During percutaneous PVE, the portal tree can be accessed via an ipsilateral approach (through the tumor-bearing liver) or the contralateral approach (through the anticipated FLR). Each approach has its advantages and disadvantages (Table 2). Advocates of the contralateral approach argue that navigating into various target portal branches is technically easier via the FLR due to the less severe angles encountered from contralateral access. In addition, the contralateral approach allows for simpler postembolization portography as the catheter is removed through the FLR [30]. The contralateral approach has also been advocated as the safest way to administer NBCA liquid embolic [24]. However, the contralateral approach requires puncture through the FLR risking damage during access. Unfortunately, when an injury (e.g., arterial pseudoaneurysm) does occur within the anticipated FLR during contralateral access, curative resection may not be possible [35].

Advocates of the ipsilateral approach argue that it is more prudent to puncture the disease-bearing liver since access site-related complications, if they occur, will occur in the liver that is to be resected. Therefore, if a major injury similar to one that was mentioned above with the contralateral approach does occur, the curative surgery still remains possible. Furthermore, the acute angles encountered with an ipsilateral approach can be overcome with reversed-curve catheters with very high technical success rates. Additionally, when segment 4 is intended to be embolized, the ipsilateral approach typically provides more direct path to this segment, which is typically the most technically demanding aspect of the procedure. One potential downside of the ipsilateral approach is that it requires a path to the portal tree that does not cross tumor, though this is rarely a problem.

• Summary & recommendations

At present, the ipsilateral approach seems to be the most prudent to avoid access-related complications within the FLR that may compromise resection. The ipsilateral approach is especially beneficial if segment 4 is to be embolized. With experience, the acute angles encountered with the ipsilateral approach are easily navigated with reverse curve catheters and now considered of little importance and consequence. If tumor burden precludes a safe access route to the right portal branches or if fast-polymerizing liquid embolics, such as NBCA, are to be utilized then the contralateral approach is a reasonable alternative.

Should chemotherapy be continued during the period between PVE & resection?

The decision to continue or suspend chemotherapy following PVE has been a topic of considerable debate. Some investigators have recommended against post-PVE chemotherapy out of concern that hepatotoxic agents would limit FLR hypertrophy. On the other hand, progression of disease is a major concern in the interim between PVE and resection and can theoretically preclude subsequent resection. In their review of 358 patients who underwent PVE before planned major hepatic resection, Shindoh *et al.* found the most common reason for not proceeding to surgery was intrahepatic or extrahepatic disease progression, accounting for over half of patients who did not proceed to surgery [34].

The recommendation to suspend chemotherapy after PVE was initially supported by a small series showing attenuated rates of hypertrophy in groups treated with PVE [36]. In this study, the ten patients treated with post-PVE chemotherapy had a significantly lower rate of hypertrophy compared with the five patients without

Table 2. Advantages/disadvantages of ipsilateral and contralateral approaches.

Ipsilateral approach	Contralateral approach
Complications during puncture occur in the liver intended to be resected ✓	Complications during puncture could damage the FLR
Limited use if rapidly polymerizing agents, such as NBCA liquid embolic, are used	Recommended if NBCA liquid embolic is used ✓
Easier access to segment 4 if this segment is to be embolized ✓	Segment 4 embolization more difficult from this approach
Acute angles require reverse-curve catheters	Easier angles to access various target branches ✓

FLR: Future liver remnant; NBCA: *n*-butyl cyanoacrylate.

post-PVE chemotherapy (median 89 vs 135 ml; $p = 0.016$).

However, subsequent larger series have showed similar rates of hypertrophy between patients treated with or without chemotherapy after PVE. Zorzi *et al.* compared patients with colorectal metastases treated with neoadjuvant chemotherapy after PVE ($n = 43$) to those who did not receive neoadjuvant chemotherapy after PVE ($n = 22$) [37]. These authors found the degree of hypertrophy to be similar between the two groups (mean 8 vs 10%, respectively; $p = 0.11$). Similarly, Covey *et al.* compared hypertrophy rates in patients treated with post-PVE neoadjuvant chemotherapy ($n = 47$) with those who did not receive chemotherapy after PVE ($n = 53$) [38]. Those treated with post-PVE chemotherapy had similar FLR growth compared with those without chemotherapy (22 vs 26%, respectively; $n = \text{NS}$).

The efficacy of post-PVE neoadjuvant chemotherapy has also been called into question. Muratore *et al.* reported on the effect of chemotherapy in 47 patients who underwent the first stage of two-stage hepatectomy, 38 of whom were treated with portal vein occlusion (PVE 27, PVL11) [39]. Out of the 47 patients, 25 patients (53.2%) received interval chemotherapy compared to 22 (46.8%) who did not receive interval chemotherapy. There was no statistically significant difference between these groups with regards to progression of disease or dropout rates after first-stage hepatectomy.

A more recent publication, however, has demonstrated tumor control with post-PVE chemotherapy. Fischer *et al.* reviewed imaging of 64 patients treated with PVE prior to resection of colorectal liver metastases [40]. They compared tumor growth in patients who received post-PVE chemotherapy ($n = 25$, 53 tumors) to those who did not receive post-PVE chemotherapy ($n = 39$, 155 tumors). Using Response Evaluation Criteria in Solid Tumors (RECIST) criteria, the authors found patients treated with post-PVE chemotherapy had improved rates of tumor control (stable or response, 81.1 vs 65.8%; $p = 0.03$). Post-PVE chemotherapy was also found to be an independent predictor of improved survival ($p < 0.006$). There was no difference in mean FLR hypertrophy between the post-PVE chemotherapy and no post-PVE chemotherapy groups (22 vs 24%, respectively; $p > 99\%$).

• Summary & recommendations

Most recent data support the use of chemotherapy post PVE, at least in the setting of colorectal metastases. The concerns that chemotherapy inhibits FLR hypertrophy have not been clearly substantiated.

Should radiation lobectomy be considered an alternative to PVE?

Radiation lobectomy refers to the transarterial lobar administration of yttrium-90 (^{90}Y) radio-embolization particles. ^{90}Y radiembolization is an established means of providing local tumor control within the liver. The unintended phenomenon of contralateral liver hypertrophy was first reported in 2008 [41]. Since then, several retrospective studies have reported a similar observation with contralateral hypertrophy ranging from 21 to 47%. This has led some authors to suggest radiation lobectomy could be used as an alternative to PVE with the added benefit of local tumor control [42].

In 2013, Vouche *et al.* reported on the rate of FLR hypertrophy after radiation lobectomy [43]. The study included 83 patients treated with right lobe radiation lobectomy. The median %FLR hypertrophy reached 45% after 9 months (range: 5–186 month; $p < 0.001$). The reported median maximum %FLR hypertrophy was 26% (range: -14 → 186). On multivariate analysis, right portal vein thrombus was the only significant correlated variable ($p = 0.02$).

Garlipp *et al.* retrospectively compared radiation lobectomy to PVE with respect to left liver hypertrophy [44]. The authors used matched-pair analysis based on the following four criteria known to influence regeneration: baseline FLR/TLV (<25 vs >25%); prior platinum-containing chemotherapy; embolization of segments 5–8 versus 4–8; and baseline platelet count (200 Gpt/l cutoff). At baseline follow-up, median 33 days for PVE and 46 days for radioembolization, the FLR volume increase was significantly greater for PVE versus radioembolization (61.5 vs 29%, $p < 0.001$).

• Summary & recommendation

In comparison to PVE, radiation lobectomy results in significantly reduced rates of FLR hypertrophy. It is, therefore, a poor substitute for PVE in patients who are already considered candidates for large volume hepatic resection at the time of diagnosis. The risk of disease progression within the FLR or at extrahepatic

sites increases with time therefore favors more rapid FLR hypertrophy rates and earlier resection. In cases of borderline resectable disease, the contralateral hypertrophy noted after radiation lobectomy may serve as an added benefit of this therapy in cases where downsizing bulky disease results in acceptable surgical planes for subsequent resection.

Is surgical PVL or ALPPS preferable to PVE?

Surgical techniques to induce FLR hypertrophy include either PVL alone or the more extensive ALPPS procedure that combines PVL with the surgical division of the hepatic parenchyma along the falciform ligament. Each of these procedures will be discussed and compared with PVE in this section.

Although seemingly more invasive than PVE, surgical PVL has been used in conjunction with other planned abdominal surgery, such as removal of colonic primary tumor, or in the first stage of a two-stage hepatectomy [45]. Studies comparing PVE to PVL have shown varying results. Robles *et al.* compared FLR hypertrophy after PVE ($n = 18$) and PVL ($n = 23$) [46]. The PVE group demonstrated greater %FLR hypertrophy compared with PVL (median: 40 vs 30%; $p < 0.05$). Capussotti *et al.* reported on the outcomes of 17 patients treated with PVL compared with 31 patients treated with PVE [45]. There were no procedure-related deaths in either group. The volumetric FLR increase in the PVL and PVE groups was similar (43.1 and 53.4%, respectively; $p = 0.39$), however, the PVL group was imaged at a significantly greater interval postocclusion compared with PVE (median: 40 vs 29 days; $p = 0.01$).

In 2015, Pandanaboyana *et al.* published a meta-analysis of PVL versus PVE [47]. The publication pooled data from seven retrospective studies with a total of 218 patients, including the publications just described. In comparing %FLR increase, the authors pooled data from three studies and found a trend toward improved hypertrophy for PVE that approached but did not meet statistical significance (39 vs 27%; $p = 0.06$). Similarly, the time between PVE or PVL and resection showed a trend toward shorter interval for PVE that approached but did not meet statistical significance (45 vs 59 days; $p = 0.06$). There was no difference between disease progression ($p = 0.81$) or postoperative liver failure ($p = 0.82$).

The ALPPS procedure gained prominence in 2012 when Schnitzbauer *et al.* reported a very

rapid increase in FLR volume after *in situ* splitting of the liver combined with PVL [48]. Interest in the procedure grew out of the prospect that a faster hypertrophy rate would allow for shorter interval to surgical resection and theoretic decrease in patient dropout due to disease progression. However, the ALPPS procedure has been associated with increased morbidity raising debate as to whether this surgical approach is justified. Despite relatively recent interest in ALPPS, there has been considerable data reported on early experience with the surgery.

In their 2012 series, Schnitzbauer *et al.* reported on 25 patients treated with the PVL and *in situ* splitting of the liver along the falciform ligament followed by resection [48]. The median FLR volume increase was 74% (range: 21–192%). The median time to subsequent resection was 9 days (range: 5–28 days). Perioperative complications were seen in 16 patients (68%) including three deaths.

In 2014, Schadde *et al.* published a meta-analysis of 13 publications reporting on 295 patients who underwent ALPPS [49]. The increase in liver volume was 84% (95% CI: 78–92%). The feasibility rate, defined as those patients who completed stage 2 resection, was reported to be 97% (95% CI: 94–99%) but only included data from six of the 13 studies. The mortality rate was 11% (95% CI: 8–16%) and morbidity of grade IIIA or higher 44% (95% CI: 38–50%).

Much lower rates of perioperative morbidity and mortality may be possible with refinements in surgical technique. In 2015, Hernandez-Alejandro *et al.* reported their prospective experience with ALPPS using refinements to the initially described technique [50]. The described surgical refinements were meant to limit ischemia to segment 4, as well as the biliary tree. In addition, all patients underwent 6–8 weeks of preoperative chemotherapy potentially selecting out patients with aggressive tumor biology who demonstrated disease progression in that interval. Fourteen patients underwent ALPPS and all were subsequently resected at a median 8 days (range: 7–10). The authors reported no patients with complications after ALPPS stage 1 and 5 patients (36%) with complications after resection. Mortality was 0% at the median follow-up of 9 months.

Even with improvement in the ALPPS complication rates, the purported benefits of the ALPPS procedure, namely improvement in

dropout rates due to disease progression, has been questioned. Although patients treated with ALPPS proceed to resection at a higher rate than after PVE, it is possible that those with tumor progression after PVE have unfavorable biology and would not have benefitted from resection [51]. In support of this, Oldhafer reported on a high tumor recurrence rate after ALPPS with six out of seven patients showing disease progression at 3-month follow-up imaging [52].

• Summary & recommendations

In comparison to PVL, PVE has been shown in individual studies to result in improved FLR hypertrophy and in meta-analysis showed a trend toward improved hypertrophy that failed statistical significance by an extremely narrow margin ($p = 0.06$). PVE is also a much less invasive procedure than surgical ligation. However, PVL may be reasonable in combination with another planned surgery (e.g., to resect a colonic primary), especially if only a modest increase in FLR is required preoperatively.

Compared to PVE, the ALPPS procedure is a much more invasive therapy with significant morbidity. Although the shorter interval to resection is enticing and seemingly lowers the dropout rate due to disease progression, it remains unclear whether these patients have microscopic disease that is not clinically evident at the time of ALPPS and therefore do not benefit from short interval resection. Additional studies are required to determine whether the recently reported lower morbidity and mortality rates of ALPPS can be replicated, as well as whether the theoretic benefit

of shorter interval resection after ALPPS truly improves disease free or overall survival.

Conclusion & future perspective

PVE is a safe and efficacious means of reducing postoperative morbidity of large volume hepatic resection and will no doubt remain an important adjunct to major hepatic resection over the next decade. Nonetheless, surgeons and interventional radiologists must still navigate the controversial issues detailed in this article. Answers to these questions are, of course, best evaluated with multicenter, prospective, randomized trials. Unfortunately, the challenges in establishing these types of trials in this multidisciplinary field make it unlikely that a majority of these issues will be definitively answered in a prospective, randomized nature. However, with widespread adoption of PVE, we expect further robust outcomes data in the coming years that will no doubt shed light on these issues. Additionally, ongoing scientific advances, whether it be molecular imaging to identify micrometastases in the FLR or newer embolic agents and delivery systems, will undoubtedly potentiate further refinements in PVE.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

- 1 Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J. Clin.* 64(1), 9–29 (2014).
- 2 Shoup M, Gonen M, D'Angelica M *et al.* Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. *J. Gastrointest. Surg.* 7(3), 325–330 (2003).
- 3 Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey JN. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. *Br. J. Surg.* 94(11), 1386–1394 (2007).
- 4 Kishi Y, Abdalla EK, Chun YS *et al.* Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. *Ann. Surg.* 250(4), 540–548 (2009).
- One of the largest series of portal vein embolization (PVE) to date.
- 5 Jaeck D, Oussoultzoglou E, Rosso E, Greget M, Weber JC, Bachellier P. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. *Ann. Surg.* 240(6), 1037–1049; discussion 1049–1051 (2004).
- 6 Abulkhir A, Limongelli P, Healey AJ *et al.* Preoperative portal vein embolization for major liver resection: a meta-analysis. *Ann. Surg.* 247(1), 49–57 (2008).
- Over 1000 patients included confirming the impressive safety profile of PVE.
- 7 Di Stefano DR, de Baere T, Denys A *et al.* Preoperative percutaneous portal vein embolization: evaluation of adverse events in 188 patients. *Radiology* 234(2), 625–630 (2005).
- Excellent detailed summary of adverse events related to PVE.

- 8 Mise Y, Sakamoto Y, Ishizawa T *et al.* A worldwide survey of the current daily practice in liver surgery. *Liver Cancer* 2(1), 55–66 (2013).
- **Demonstrates the worldwide adoption of this procedure.**
- 9 Fausto N, Campbell JS, Riehle KJ. Liver regeneration. *Hepatology* 43(2 Suppl. 1), S45–S53 (2006).
- 10 Schweizer W, Duda P, Tanner S *et al.* Experimental atrophy/hypertrophy complex (AHC) of the liver: portal vein, but not bile duct obstruction, is the main driving force for the development of AHC in the rat. *J. Hepatol.* 23(1), 71–78 (1995).
- 11 May BJ, Talenfeld AD, Madoff DC. Update on portal vein embolization: evidence-based outcomes, controversies, and novel strategies. *J. Vasc. Interv. Radiol.* 24(2), 241–254 (2013).
- **A comprehensive up-to-date review of the field.**
- 12 Nagino M, Nimura Y, Kamiya J *et al.* Changes in hepatic lobe volume in biliary tract cancer patients after right portal vein embolization. *Hepatology* 21(2), 434–439 (1995).
- 13 Taub R. Liver regeneration: from myth to mechanism. *Nat. Rev. Mol. Cell Biol.* 5(10), 836–847 (2004).
- 14 Yamanaka N, Okamoto E, Kawamura E *et al.* Dynamics of normal and injured human liver regeneration after hepatectomy as assessed on the basis of computed tomography and liver function. *Hepatology* 18(1), 79–85 (1993).
- 15 Dixon E, Abdalla E, Schwarz RE, Vauthey JN. AHPBA/SSO/SSAT sponsored Consensus Conference on Multidisciplinary Treatment of Hepatocellular Carcinoma. *HPB (Oxford)* 12(5), 287–288 (2010).
- **Multidisciplinary consensus recommendations for hepatocellular carcinoma that includes PVE.**
- 16 de Meijer VE, Kalish BT, Puder M, Ijzermans JN. Systematic review and meta-analysis of steatosis as a risk factor in major hepatic resection. *Br. J. Surg.* 97(9), 1331–1339 (2010).
- 17 Vauthey JN, Pawlik TM, Ribero D *et al.* Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J. Clin. Oncol.* 24(13), 2065–2072 (2006).
- 18 Farges O, Belghiti J, Kianmanesh R *et al.* Portal vein embolization before right hepatectomy: prospective clinical trial. *Ann. Surg.* 237(2), 208–217 (2003).
- 19 Vauthey JN, Abdalla EK, Doherty DA *et al.* Body surface area and body weight predict total liver volume in Western adults. *Liver Transpl.* 8(3), 233–240 (2002).
- 20 Johnson TN, Tucker GT, Tanner MS, Rostami-Hodjegan A. Changes in liver volume from birth to adulthood: a meta-analysis. *Liver Transpl.* 11(12), 1481–1493 (2005).
- 21 Shah A, Goffette P, Hubert C *et al.* Comparison of different methods to quantify future liver remnants after preoperative portal vein embolization to predict postoperative liver failure. *Hepatogastroenterology* 58(105), 109–114 (2011).
- 22 Madoff DC, Abdalla EK, Gupta S *et al.* Transhepatic ipsilateral right portal vein embolization extended to segment IV: improving hypertrophy and resection outcomes with spherical particles and coils. *J. Vasc. Interv. Radiol.* 16(2 Pt 1), 215–225 (2005).
- 23 Shimamura T, Nakajima Y, Une Y *et al.* Efficacy and safety of preoperative percutaneous transhepatic portal embolization with absolute ethanol: a clinical study. *Surgery* 121(2), 135–141 (1997).
- 24 Denys A, Lacombe C, Schneider F *et al.* Portal vein embolization with *n*-butyl cyanoacrylate before partial hepatectomy in patients with hepatocellular carcinoma and underlying cirrhosis or advanced fibrosis. *J. Vasc. Interv. Radiol.* 16(12), 1667–1674 (2005).
- 25 Bent CL, Low D, Matson MB, Renfrew I, Fotheringham T. Portal vein embolization using a nitinol plug (amplatzer vascular plug) in combination with histoacryl glue and iodized oil: adequate hypertrophy with a reduced risk of nontarget embolization. *Cardiovasc. Interv. Radiol.* 32(3), 471–477 (2009).
- 26 de Baere T, Denys A, Paradis V. Comparison of four embolic materials for portal vein embolization: experimental study in pigs. *Eur. Radiol.* 19(6), 1435–1442 (2009).
- 27 Tsoumakidou G, Theocharis S, Ptohis N *et al.* Liver hypertrophy after percutaneous portal vein embolization: comparison of *n*-butyl-2-cyanoacrylate versus sodium acrylate-vinyl alcohol copolymer particles in a swine model. *Cardiovasc. Interv. Radiol.* 34(5), 1042–1049 (2011).
- 28 Guiu B, Bize P, Gunther D, Demartines N, Halkic N, Denys A. Portal vein embolization before right hepatectomy: improved results using *n*-butyl-cyanoacrylate compared with microparticles plus coils. *Cardiovasc. Interv. Radiol.* 36(5), 1306–1312 (2013).
- 29 Mise Y, Aloia TA, Conrad C, Huang SY, Wallace MJ, Vauthey JN. Volume regeneration of segments 2 and 3 after right portal vein embolization in patients undergoing two-stage hepatectomy. *J. Gastrointest. Surg.* 19(1), 133–141; discussion 141 (2015).
- 30 Denys A, Prior J, Bize P *et al.* Portal vein embolization: what do we know? *Cardiovasc. Interv. Radiol.* 35(5), 999–1008 (2012).
- 31 Capussotti L, Muratore A, Ferrero A, Anselmetti GC, Corgnier A, Regge D. Extension of right portal vein embolization to segment IV portal branches. *Arch. Surg.* 140(11), 1100–1103 (2005).
- 32 Kishi Y, Madoff DC, Abdalla EK *et al.* Is embolization of segment 4 portal veins before extended right hepatectomy justified? *Surgery* 144(5), 744–751 (2008).
- 33 de Baere T, Teriitshau C, Deschamps F *et al.* Predictive factors for hypertrophy of the future remnant liver after selective portal vein embolization. *Ann. Surg. Oncol.* 17(8), 2081–2089 (2010).
- 34 Shindoh J, Vauthey JN, Zimmiti G *et al.* Analysis of the efficacy of portal vein embolization for patients with extensive liver malignancy and very low future liver remnant volume, including a comparison with the associating liver partition with portal vein ligation for staged hepatectomy approach. *J. Am. Coll. Surg.* 217(1), 126–133; discussion 133–124 (2013).
- 35 Kodama Y, Shaw CM, Madoff DC. Complications of portal vein embolization. In: *Venous Embolization of the Liver: Radiologic and Surgical Practice*. Madoff DC, Makuuchi M, Nagino M, Vauthey JN (Eds). Springer-Verlag, London, UK, 159–168 (2011).
- 36 Beal IK, Anthony S, Papadopolou A *et al.* Portal vein embolisation prior to hepatic resection for colorectal liver metastases and the effects of perioperative chemotherapy. *Br. J. Radiol.* 79(942), 473–478 (2006).
- 37 Zorzi D, Chun YS, Madoff DC, Abdalla EK, Vauthey JN. Chemotherapy with bevacizumab does not affect liver regeneration after portal vein embolization in the treatment of colorectal liver metastases. *Ann. Surg. Oncol.* 15(10), 2765–2772 (2008).
- 38 Covey AM, Brown KT, Jarnagin WR *et al.* Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. *Ann. Surg.* 247(3), 451–455 (2008).
- 39 Muratore A, Zimmiti G, Ribero D, Mellano A, Viganò L, Capussotti L. Chemotherapy

- between the first and second stages of a two-stage hepatectomy for colorectal liver metastases: should we routinely recommend it? *Ann. Surg. Oncol.* 19(4), 1310–1315 (2012).
- 40 Fischer C, Melstrom LG, Arnaoutakis D *et al.* Chemotherapy after portal vein embolization to protect against tumor growth during liver hypertrophy before hepatectomy. *JAMA Surg.* 148(12), 1103–1108 (2013).
- **Demonstrates the efficacy of chemotherapy following PVE in colorectal liver metastases.**
- 41 Jakobs TF, Saleem S, Atassi B *et al.* Fibrosis, portal hypertension, and hepatic volume changes induced by intra-arterial radiotherapy with 90yttrium microspheres. *Dig. Dis. Sci.* 53(9), 2556–2563 (2008).
- 42 Gulec SA, Pennington K, Hall M, Fong Y. Preoperative y-90 microsphere selective internal radiation treatment for tumor downsizing and future liver remnant recruitment: a novel approach to improving the safety of major hepatic resections. *World J. Surg. Oncol.* 7, 6 (2009).
- 43 Vouche M, Lewandowski RJ, Atassi R *et al.* Radiation lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. *J. Hepatol.* 59(5), 1029–1036 (2013).
- 44 Garlipp B, de Baere T, Damm R *et al.* Left-liver hypertrophy after therapeutic right-liver radioembolization is substantial but less than after portal vein embolization. *Hepatology* 59(5), 1864–1873 (2014).
- 45 Capussotti L, Muratore A, Baracchi F *et al.* Portal vein ligation as an efficient method of increasing the future liver remnant volume in the surgical treatment of colorectal metastases. *Arch. Surg.* 143(10), 978–982; discussion 982 (2008).
- 46 Robles R, Marin C, Lopez-Conesa A, Capel A, Perez-Flores D, Parrilla P. Comparative study of right portal vein ligation versus embolisation for induction of hypertrophy in two-stage hepatectomy for multiple bilateral colorectal liver metastases. 38(7), 586–593 (2012).
- 47 Pandanaboyana S, Bell R, Hidalgo E *et al.* A systematic review and meta-analysis of portal vein ligation versus portal vein embolization for elective liver resection. *Surgery* 157(4), 690–698 (2015).
- 48 Schnitzbauer AA, Lang SA, Goessmann H *et al.* Right portal vein ligation combined with *in situ* splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. *Ann. Surg.* 255(3), 405–414 (2012).
- 49 Schadde E, Ardiles V, Slankamenac K *et al.* ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumors compared with conventional-staged hepatectomies: results of a multicenter analysis. *World J. Surg.* 38(6), 1510–1519 (2014).
- 50 Hernandez-Alejandro R, Bertens KA, Pineda-Solis K, Croome KP. Can we improve the morbidity and mortality associated with the associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) procedure in the management of colorectal liver metastases? *Surgery* 157(2), 194–201 (2015).
- 51 Aloia TA, Vauthey JN. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): what is gained and what is lost? *Ann. Surg.* 256(3), e9; author reply e16–e19 (2012).
- 52 Oldhafer KJ, Donati M, Jenner RM, Stang A, Stavrou GA. ALPPS for patients with colorectal liver metastases: effective liver hypertrophy, but early tumor recurrence. *World J. Surg.* 38(6), 1504–1509 (2014).
- **Highlights a potential pitfall of early resection potentiated by associated liver partition and portal vein ligation.**