

Update on Portal Vein Embolization: Evidence-based Outcomes, Controversies, and Novel Strategies

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ABSTRACT

Portal vein embolization (PVE) is an established therapy used to redirect portal blood flow away from the tumor-bearing liver to the anticipated future liver remnant (FLR) and usually results in FLR hypertrophy. PVE is indicated when the FLR is considered too small before surgery to support essential function after surgery. When appropriately applied, PVE reduces postoperative morbidity and increases the number of patients eligible for curative hepatic resection. PVE also has been combined with other therapies to improve patient outcomes. This article assesses more recent outcomes data regarding PVE, reviews the existing controversies, and reports on novel strategies currently being investigated.

ABBREVIATIONS

BSA = body surface area, FLR = future liver remnant, HCC = hepatocellular carcinoma, HVE = hepatic vein embolization, PVE = portal vein embolization, PVL = portal vein ligation, TAE = transarterial embolization, TELV = total estimated liver volume

Rates of primary liver cancer have continued to increase dramatically over the past decade in the United States, and the liver remains a common site of metastases (1). Surgical resection of primary tumors and metastases confined to the liver is the mainstay of curative therapy. Owing to the liver's unique ability to regenerate, most of the organ can be resected if indicated. However, major hepatic resection places patients at risk for developing complications related to liver insufficiency, particularly in the perioperative period, before the liver has had time to regenerate. Although causes of postoperative liver insufficiency are multifactorial, the anticipated volume of liver that remains after surgery, termed the future liver remnant (FLR), has been shown to be a strong independent predictor of postoperative complications (2,3).

Portal vein embolization (PVE) is an established image-guided procedure that has been adopted worldwide (4). Embolization of portal branches feeding tumor-bearing segments leads to concomitant atrophy of these segments and hypertrophy of the FLR (5). This procedure has been

shown to reduce postoperative complications and increase the number of patients able to undergo surgery with curative intent (6,7). Since the last review published in this journal (8), additional experience and outcomes data have further delineated the role of PVE. In addition, PVE has been combined with other therapies to improve hypertrophy and expand the treatment options available to patients. This article reviews the most recent data regarding PVE and presents novel combination therapies currently being investigated.

PATHOPHYSIOLOGY AND MECHANISM OF ACTION

The pathophysiology, rationale, and basic technical considerations of PVE have been previously described (8,9). However, it is worthwhile to review the key concepts because they provide a basis for more recent developments.

After hepatic injury or partial resection, changes in both hemodynamics and metabolic pathways stimulate regeneration of noninjured segments, with the portal vein playing a central role in transporting trophic factors (10–12). Regeneration on a cellular level begins within hours, and most patients achieve adequate regeneration within a few weeks (13,14). However, patients with underlying liver damage, particularly cirrhosis, can demonstrate attenuated rates and degrees of hypertrophy (15). Regeneration after PVE typically occurs at a slower rate compared with hepatectomy (ie, greater stimulus for FLR growth when

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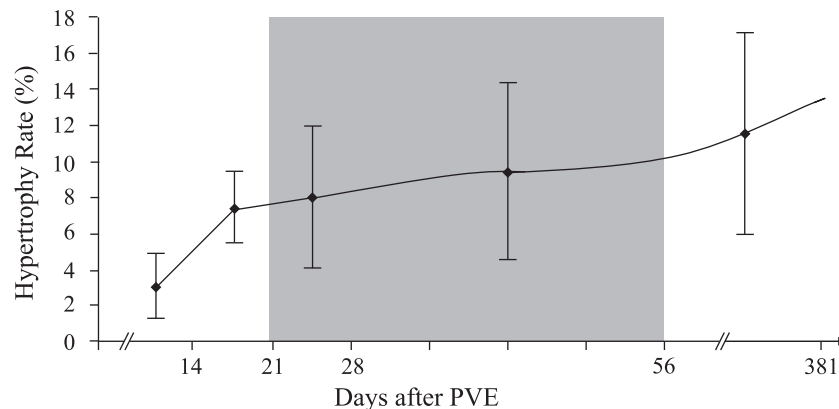


Figure 1. Degree of hypertrophy of the standardized FLR over time after PVE with kinetics of FLR growth, plotted as median (with interquartile ranges) degree of hypertrophy after PVE. The shaded zone (days 22–56 after PVE) identifies the “plateau” period during which the degree of hypertrophy did not change significantly between measurement points. (Used with permission from Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey J-N. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. *Br J Surg* 2007; 94:1386–1394.)

liver parenchyma is removed rather than subjected to embolization) (Fig 1). In contrast to the postembolization syndrome common with transarterial therapy, which results from necrosis, the apoptosis-mediated cell death resulting from PVE is known to cause minimal pain and fever (16).

Makuuchi et al (17) were the first to describe the use of PVE as a means of improving surgical outcomes by preventing perioperative liver insufficiency. Subsequent studies have shown that increased FLR volume is associated with improved biliary excretion, albumin uptake, and postoperative liver function (18–20).

PVE has traditionally been performed via one of three approaches, termed transileocolic, contralateral, and ipsilateral approaches. The oldest, the transileocolic approach, is a surgical procedure performed in the operating room under general anesthesia. After performing a right lower quadrant incision, a major ileocolic venous branch is accessed via direct puncture allowing for catheter manipulation to the portal vein. This approach has the advantage of avoiding puncture through the liver. However, this surgical procedure has generally been replaced by the less invasive percutaneous contralateral and ipsilateral techniques, which are performed using ultrasound-guided transhepatic puncture. The contralateral approach accesses the portal system via the FLR. This technique allows for easier catheter manipulation to the tumor-bearing liver because of fewer acute angles between access and target portal branches. However, the contralateral approach risks damage to the FLR during access and catheter manipulation.

The ipsilateral approach involves percutaneous access through the tumor-bearing liver, avoiding potential damage to the FLR during instrumentation. The acute angles necessary for embolization of adjacent liver segments can be overcome using reverse curve catheters. Care must be taken to avoid access through tumor to prevent peritoneal seeding. If a safe route is not visualized, the contralateral approach remains a reasonable alternative.

EVALUATION OF PATIENTS CONSIDERED FOR HEPATECTOMY

PVE is indicated when the FLR is either too small or borderline in size to support essential hepatic function. However, the absolute size of the FLR does not accurately predict which patients are at risk for liver insufficiency because larger patients require larger volumes of liver to support function. A standardized FLR, expressed as a percentage of FLR in relation to total functioning liver volume, allows for a more accurate assessment of FLR and comparison of outcomes data between patients of varying sizes (2).

To calculate the standardized FLR, volumes of the FLR and total functioning liver volume must be obtained. Typically, FLR volume is measured directly using cross-sectional volumetric software. Computed tomography (CT) volumetry can also be used to measure total liver; however, this requires exclusion of tumor volume from the overall liver volume. Measuring tumor volume can be tedious and imprecise, particularly when tumor burden is extensive.

Alternatively, the total estimated liver volume (TELV) can be calculated based on the close relationship between body surface area (BSA) and liver volume. Vauthey et al (21) derived the following formula for estimating liver volume by analyzing liver size and BSA in 292 Western adults.

$$\text{TELV} = -794.41 + 1,267.28 (\text{BSA})$$

A third method of calculating standardized FLR uses body weight, rather than BSA, to determine the TELV. Although multiple similar formulas exist in the literature, a meta-analysis published in 2005 determined the Vauthey formula to be least biased and most accurate for adults (22). Although Chun et al (23) later found the body weight method to be equally as predictive as BSA, a more recent study comparing direct volumetric liver measurement and estimated liver volume based on BSA found the TELV method to be superior ($P < .005$) (24).

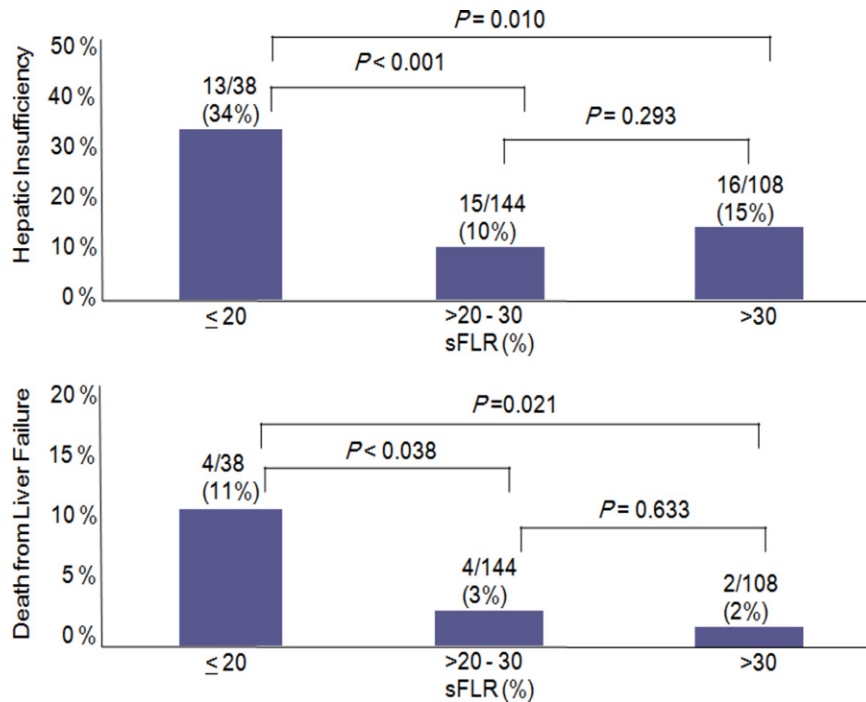


Figure 2. Rates of (a) hepatic insufficiency and (b) death by preoperative standardized FLR (sFLR) volume. (Adapted with permission from Kishi Y, Abdalla EK, Chun YS, et al. Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. *Ann Surg* 2009; 250:540–548.) (Available in color online at www.jvir.org.)

EVIDENCE-BASED INDICATIONS

Multiple factors are considered when deciding which patients would benefit from PVE, including baseline liver function, standardized FLR, and complexity of the planned surgery. In recent years, substantial outcomes data have been reported allowing for better defined indications for PVE. In patients with normal liver function, a standardized FLR of 10% can support essential hepatic function; however, standardized FLR < 20% is associated with increased postoperative complications (25). Kishi et al (7) published a series of 301 consecutive patients who underwent extended right hepatectomy. They found that patients with a preoperative standardized FLR < 20% had significantly higher rates of postoperative liver insufficiency and death from liver failure compared with patients with standardized FLR ≥ 20% ($P < .05$) (Fig 2a and b). In addition, patients who underwent PVE before surgery to increase their standardized FLR from < 20% to > 20% had statistically equivalent rates of liver insufficiency as patients with > 20% at baseline. Ribero et al (3) found that both standardized FLR < 20% and degree of standardized FLR hypertrophy after PVE < 5% predicted outcome after resection (Fig 3). Based on these results and other supporting publications (25,26), a Consensus Conference on the Multidisciplinary Treatment of Hepatocellular Cancer in 2010 recommended PVE for standardized FLR < 20% in patients with preserved liver function (27).

Higher standardized FLR cutoffs are considered for patients with additional risk factors such as hepatic steatosis, hepatotoxic chemotherapy exposure, and compensated

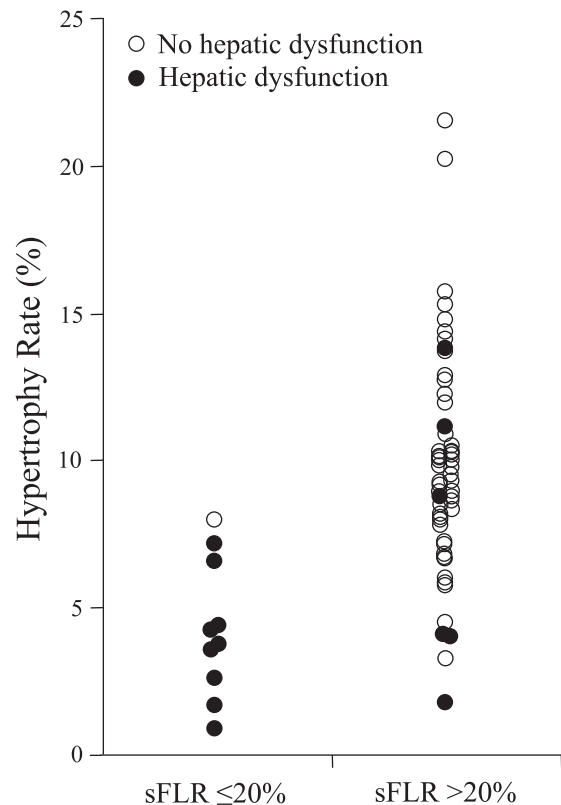


Figure 3. Presence of hepatic dysfunction by standardized FLR (sFLR) volume and degree of hypertrophy. (Used with permission from Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey J-N. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. *Br J Surg* 2007; 94:1386–1394.)

cirrhosis. Multiple studies have shown an increased risk of postoperative complications in patients with hepatic steatosis (28–30). In a meta-analysis of four studies involving 1,000 patients, de Meijer et al (31) found that patients with > 30% steatosis had significantly higher risk of postoperative complications and postoperative death compared with patients without steatosis (relative risk and 95% confidence interval 2.01 and 1.66–2.44 vs 2.79 and 1.19–6.51). Similarly, patients who have been exposed to hepatotoxic chemotherapy have been shown to be at increased risk for postoperative complications. Pawlik et al (32) reviewed the outcomes of 212 patients who underwent resection for colorectal metastases; 173 of the patients received preoperative chemotherapy. Oxaliplatin was associated with grade 3 sinusoidal dilation ($P = .017$), and irinotecan was associated with steatohepatitis. Vauthey et al (33) found the same associations of oxaliplatin with sinusoidal dilation ($P < .001$) and irinotecan with steatohepatitis. In their review, steatohepatitis was associated with an increased 90-day mortality ($P = .001$). Based on these results, many authors consider PVE when standardized FLR is < 30% in patients with either hepatic steatosis or significant exposure to hepatotoxic chemotherapy.

Cirrhosis is another risk factor that is given serious consideration before hepatic resection. Patients with advanced cirrhosis are not considered for hepatic resection. For patients with well-compensated cirrhosis (ie, Child-Pugh class A) who are considered for resection, a standardized FLR > 40% is recommended. This recommendation is supported by a prospective alternative allocation trial in which 28 patients with chronic liver disease were allocated

to PVE or no PVE before resection (34). The mean standardized FLR size in the PVE group was 35%. The PVE group had a significantly lower incidence of pulmonary complications, ascites, and liver failure.

Although the above-discussed recommendations are useful when considering patients for PVE, additional factors such as patient age, comorbidities, and complexity of planned surgery are also considered. Until additional evidence-based criteria are defined further, the decision to perform PVE is made on a case-by-case basis. Optimally, an interdisciplinary team should be involved in deciding when PVE is appropriate.

COMPLICATIONS

Complications of PVE are similar to other image-guided transhepatic procedures. Complications include subcapsular hematoma, bile duct damage, hemoperitoneum, and cholangitis. In addition, PVE-specific complications include nontarget embolization, recanalization of segments that received embolization, and complete portal vein thrombosis. In 2010, the Society of Interventional Radiology established quality improvement guidelines for transcatheter embolization, including a suggested threshold for PVE-related major complications of 6% and threshold for PVE-related morbidity of 11% (35).

Most published complication rates are well below this range. A meta-analysis published in 2008 pooled data from 37 studies from 1990–2005 involving 1,088 patients (36). Percutaneous PVE was performed in most cases (72%), with

Table 1. Complication Rates for Portal Vein Embolization Reviewed in Literature

| Reference | Number of Patients; Complication Rate | Complication Type | Number |
|---------------------------------|---|--------------------------------------|--------|
| Kodama et al (2002) (38) | 47 patients; 7 (15%) complications | Pneumothorax | 2 |
| | | Subcapsular hematoma | 2 |
| | | Arterial puncture | 1 |
| | | Pseudoaneurysm | 1 |
| | | Hemobilia | 1 |
| | | Portal vein thrombus | 1 |
| | | Migration of embolic material to FLR | 10 |
| Di Stefano et al (2005) (37) | 188 patients; 24 (12.8%) adverse events | Transient liver failure | 6 |
| | | Occlusion of portal vein | 3 |
| | | Subcapsular hematoma | 2 |
| | | Hemobilia | 1 |
| | | Hemoperitoneum | 1 |
| | | Rupture of gallbladder metastasis | 1 |
| | | Liver abscess | 3 |
| Abulkhir et al (2008) (36) | Meta-analysis of 37 studies involving 1,088 patients; reported morbidity 2.2% | Cholangitis | 2 |
| | | Left or main portal vein thrombus | 2 |
| | | Subcapsular hematoma | 2 |
| | | Portal hypertension | 1 |
| | | Septic necrosis | 1 |

FLR = future liver remnant.

the transileocolic technique used in the remaining cases. The overall pooled morbidity was 2.2% with 0% procedure-related mortality. Di Stefano et al (37) reviewed the records of 188 patients who underwent PVE via the contralateral approach resulting in 24 (12.8%) adverse events without mortality. Transient liver failure occurred at a significantly higher rate in patients with cirrhosis (5 of 30; $P < .001$). Kodama et al (38) reviewed 47 percutaneous PVE procedures in 46 patients (11 via contralateral approach). Complications occurred more frequently in the punctured lobe leading the authors to recommend the ipsilateral approach. The specific complications reported in these studies are listed in **Table 1**.

PVE TECHNIQUE MODIFICATIONS AND COMBINATION STRATEGIES

Sequential Arterial and Portal Embolization

Transcatheter arterial chemoembolization is an established therapy used to provide locoregional control of unresectable hepatocellular carcinoma (HCC) and as a bridge to transplant (39). In addition, this therapy has been applied in sequence with PVE before hepatectomy for HCC (**Fig 4a–g**). There are several theoretical benefits to this combined approach. HCC typically arises in a background of advanced liver disease presenting challenges for resection. Because of increased postoperative complication rates, patients with cirrhosis require a relatively robust FLR to be considered amenable to resection; if standardized FLR is $< 40\%$, PVE is indicated. Additionally, as previously discussed, cirrhotic livers often demonstrate decreased propensity to regenerate and require prolonged time intervals to achieve satisfactory hypertrophy. Transcatheter arterial chemoembolization performed before PVE results in a greater inflammatory response, which is known to contribute to liver regeneration (40). In addition, HCC preferentially derives its blood supply from the hepatic artery. After PVE, there is a compensatory increase in hepatic artery flow, termed the hepatic artery buffer response, which can lead to accelerated tumor growth (41). Locoregional control offered by transcatheter arterial chemoembolization may prevent progression of disease during the interval between PVE and resection. Finally, HCC is associated with the development of arteriportal shunts, which can mitigate the effects of PVE (32). Embolization of these arteriportal shunts is performed during transcatheter arterial chemoembolization.

Aoki et al (42) published a retrospective review of 17 patients who underwent sequential transcatheter arterial chemoembolization and PVE, 16 of whom subsequently underwent resection. PVE was performed a median of 9 days after transcatheter arterial chemoembolization (range, 4–44 days). Transient increases in liver enzyme and bilirubin levels returned to baseline after several days following both transcatheter arterial chemoembolization and PVE. There was no procedural mortality and a 25%

minor complication rate. The standardized FLR increased significantly after PVE to a median of 51% (range, 39%–68%; $P < .01$). One patient did not undergo resection because of an increase of the percent of indocyanine green retained by the liver at 15 minutes from 17% to 28%. The 5-year overall survival after curative intent resection was 55.6%, and 5-year disease-free survival after resection was 46.7%.

In 2006, Ogata et al (43) published a retrospective analysis of 36 patients with HCC and cirrhosis who underwent resection after PVE; 18 of the patients had transcatheter arterial chemoembolization 3 weeks before PVE. The transcatheter arterial chemoembolization plus PVE group demonstrated a greater mean increase in FLR volume compared with the PVE alone group (12.5% vs 8.4%; $P = .022$). The transcatheter arterial chemoembolization plus PVE group also demonstrated an increased incidence of complete tumor necrosis (15 of 18 vs 1 of 18; $P < .001$) and a higher 5-year disease-free survival (37% vs 19%; $P = .041$).

More recently, Yoo et al (44) reported their results of 135 patients with HCC; 71 patients underwent transcatheter arterial chemoembolization plus PVE, and 64 underwent PVE only before right hepatectomy. PVE was performed an average of 1.2 months after transcatheter arterial chemoembolization. Liver function tests transiently worsened before returning to baseline in most patients; however, one patient (1 of 71; 1.4%) developed persistently elevated transaminase levels and did not undergo resection. The remaining patients had successful resections. Compared with the PVE only group, the transcatheter arterial chemoembolization plus PVE group demonstrated a higher mean increase in FLR (7.3% vs 5.8%; $P = .035$) and improved overall ($P = .028$) and recurrence-free ($P = .001$) survival (comparison using the log-rank test). The 1-year, 3-year, 5-year, and 10-year cumulative survival rates for the transcatheter arterial chemoembolization plus PVE group were 97%, 83%, 72%, and 58% compared with 89%, 73%, 56%, and 31% for the PVE only group. The 1-year, 3-year, 5-year, and 10-year recurrence-free survival rates for the transcatheter arterial chemoembolization plus PVE group were 83%, 70%, 61%, and 56% compared with 62%, 51%, 38%, and 24% for the PVE only group. The authors concluded that sequential transcatheter arterial chemoembolization and PVE is a safe and effective therapy for increasing the rate of hypertrophy of the FLR and is associated with longer recurrence-free survival.

Combination Therapy after Inadequate FLR Hypertrophy

Although PVE typically leads to reliable rates of hypertrophy, liver regeneration can be variable, especially when comorbidities such as underlying hepatic dysfunction or diabetes are present. When FLR hypertrophy is inadequate after PVE, adjunct therapies such as arterial embolization or hepatic vein embolization (HVE) can be performed.

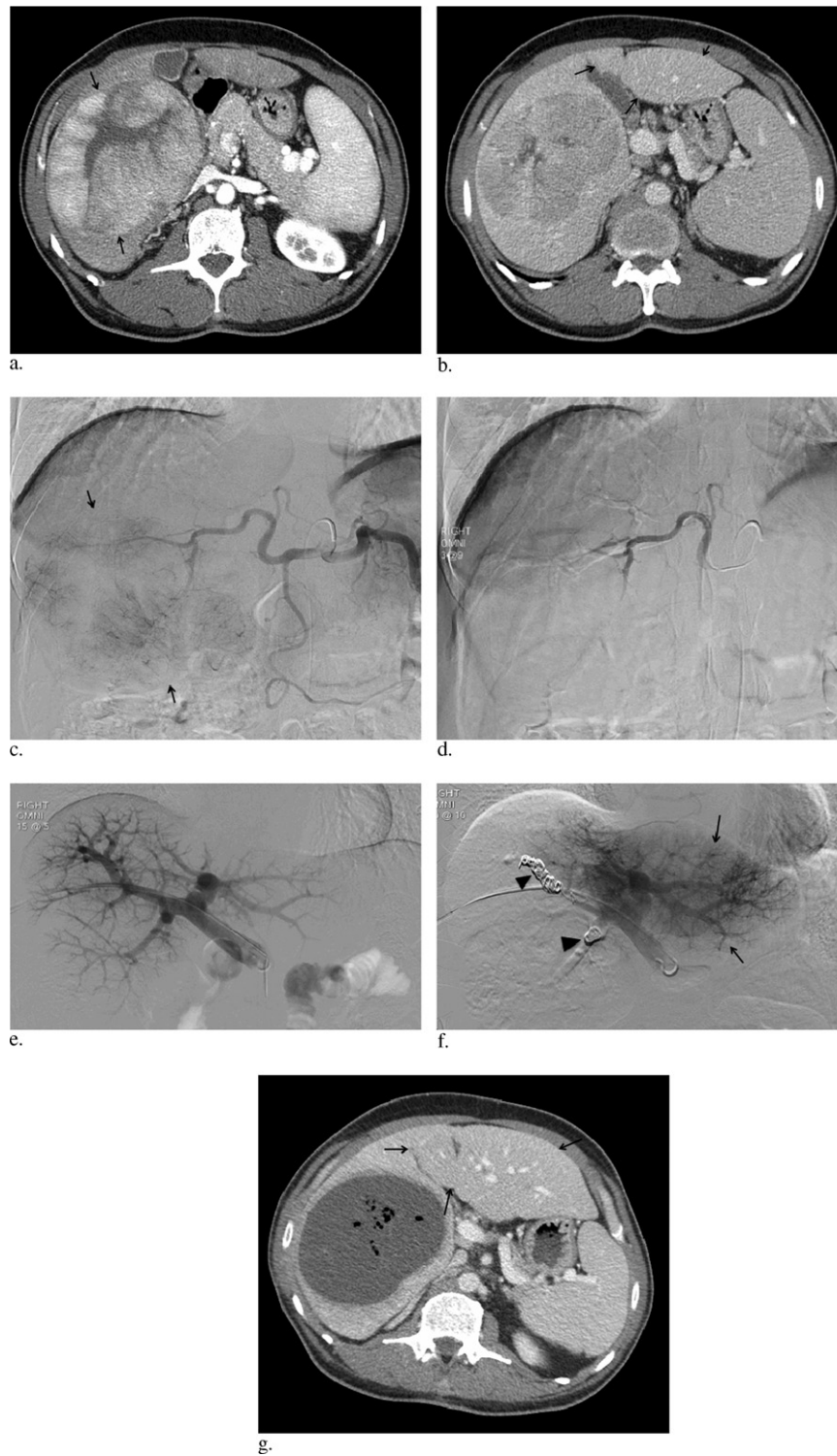


Figure 4. Combined transcatheter arterial hepatic embolization and transhepatic ipsilateral right PVE using tris-acryl particles and coils in a 56-year-old man with a history of human immunodeficiency virus, hepatitis C, and HCC. **(a)** Contrast-enhanced axial CT image shows a large mass in the right hepatic lobe (arrows). **(b)** Contrast-enhanced axial CT image shows marginal FLR (FLR/TELV = 30%) (arrows). **(c)** Anteroposterior subtracted angiographic image from the celiac axis shows a large hypervascular mass (arrows). **(d)** Arteriography performed immediately after bland embolization with 40- μ m microspheres shows complete stasis of the tumor vasculature. **(e)** Anteroposterior flush portogram obtained 4 weeks later shows a 6-F vascular sheath in a right portal vein branch and a 5-F flush catheter within the main portal vein. **(f)** Final portal venogram shows occlusion of the portal vein branches to segments 5–8 (arrowheads) with continued patency of the veins supplying the left liver (arrows). **(g)** Contrast-enhanced CT image obtained 1 month after right PVE shows substantial atrophy of the right liver, complete necrosis of the tumor, and FLR hypertrophy (FLR/TELV = 54%). The FLR is depicted by the arrows. The degree of hypertrophy is 24%. The patient successfully underwent a right hepatectomy.

Transarterial embolization (TAE), or bland embolization, has been used in the setting of inadequate FLR hypertrophy following PVE. This therapy adds a component of inflammation and necrosis, both of which are known to stimulate liver hypertrophy. Arterial embolization alone has been shown to induce hypertrophy of the FLR, although to a lesser degree compared with PVE (45).

In 2000, Nagino et al (46) first described the use of TAE to improve FLR volume in two patients with cholangiocarcinoma who demonstrated inadequate hypertrophy after PVE. In both patients, PVE in the setting of underlying liver disease led to negligible hypertrophy of the FLR at 58 days (patient 1) and 14 days (patient 2). TAE with ethanol was performed on 50% of the liver intended to be resected. The FLR volume increased from 470 mL to 685 mL (46%) 2 weeks after TAE (patient 1) and from 649 mL to 789 mL (22%) 3 weeks after TAE (patient 2). Both patients experienced postembolization syndrome with fever and abdominal pain. TAE after PVE was complicated by prolonged abnormal liver function tests (patient 1), which returned to baseline after 2 weeks, and liver abscess (patient 2), which required percutaneous drainage. Pathology showed extensive necrosis in the segments targeted by TAE.

In 2006, Gruttadauria et al (47) reported on the use of TAE to improve FLR hypertrophy after PVE for colorectal metastasis. In this report, TAE was performed with microparticles and absorbable gelatin sponge (Gelfoam) (patient 1) and microparticles and coils (patient 2) after FLR hypertrophy was deemed inadequate 6 weeks following PVE. In patient 1, FLR increased from 379 cm³ to 505 cm³ after PVE, with subsequent increase to 916 cm³ 3 weeks after TAE. In patient 2, FLR increased from 302 cm³ to 344 cm³ after PVE, with a subsequent increase to 521 cm³ 3 weeks after TAE. Complications were not reported. TAE resulted in improved hypertrophy allowing for subsequent hepatic resection.

Selective HVE has also been used to provide additional stimulus for regeneration when FLR hypertrophy is inadequate. Hwang et al (48) conducted a prospective trial postulating that occlusion of the hepatic veins draining the tumor-bearing liver could lead to increased hypertrophy of the FLR. Patients were included for selective HVE if FLR hypertrophy was deemed inadequate by volumetric CT analysis 2 weeks after PVE. Coil embolization of the right hepatic vein was performed with either an inferior vena cava filter or vascular plug placed proximally to prevent coil migration. Of the 12 patients who were treated with HVE, two patients failed to demonstrate adequate FLR hypertrophy for resection. One patient had inadvertent embolization of the hepatic vein draining the FLR and ultimately did not undergo resection.

Two-stage Hepatectomy and PVE

Surgical resection of colorectal liver metastasis is associated with long-term survival and is potentially curative

when complete resection is feasible. However, only 20%–30% of patients are considered resectable, most often because of bilobar pattern of disease. Two-stage hepatectomy, using hypertrophy of PVE, has been developed to increase the number of patients with bilobar colorectal liver metastasis amenable to resection (49). During the first stage of treatment, tumor within the projected FLR is resected or in some cases ablated. When the FLR is cleared of tumor, PVE can be performed to increase the FLR volume. PVE is typically performed between hepatic resections to improve FLR volume, particularly because these patients have usually been exposed to hepatotoxic neoadjuvant chemotherapy. In some cases, surgical portal vein ligation (PVL) during the first-stage surgery is performed rather than PVE; however, this practice is controversial, as discussed later. When adequate FLR hypertrophy is achieved, the second-stage hepatectomy targets the remainder of liver metastases, typically requiring a right or extended right hepatectomy.

Narita et al (50) reported on the outcome of 80 patients with colorectal liver metastasis scheduled for two-stage hepatectomy; 61 patients completed second-stage resection. The main reason for not completing the second-stage surgery was tumor progression (16 of 80; 20%). Of the 61 patients who completed therapy, all but 3 incorporated PVE (*n* = 55) or surgical PVL (*n* = 3). For patients completing two-stage hepatectomy, 5-year overall survival was 32%, and overall median survival was 39.6 months.

Brouquet et al (51) reported on the outcome of 65 patients with colorectal metastases who underwent first-stage hepatectomy; 47 completed the second-stage resection. This study also compared these outcomes with nonsurgical patients with disease confined to the liver who also demonstrated an objective response to systemic chemotherapy. This analysis was intended to eliminate potential selection bias because two-stage resection was offered only to patients who showed a response to modern chemotherapeutic regimens. The overall 5-year survival rate of the surgical group was 51% compared with 15% for the medical group (*P* = .005). For the 47 patients who completed the second-stage resection, 5-year survival was improved to 64%. Most of two-stage hepatectomy procedures included PVE. The authors concluded that although the surgical group benefited from improvements in systemic chemotherapy, resection conferred a clear additional survival benefit.

CONTROVERSIES

Combined Right and Segment 4 PVE

Before extended right hepatectomy, some authors have argued for extending right PVE to include segment 4 as a means of improving hypertrophy of segments 2 and 3 (Fig 5a–f) (46). However, catheter manipulation into branches feeding segment 4 is more technically demanding, and inadvertent reflux of embolic material to

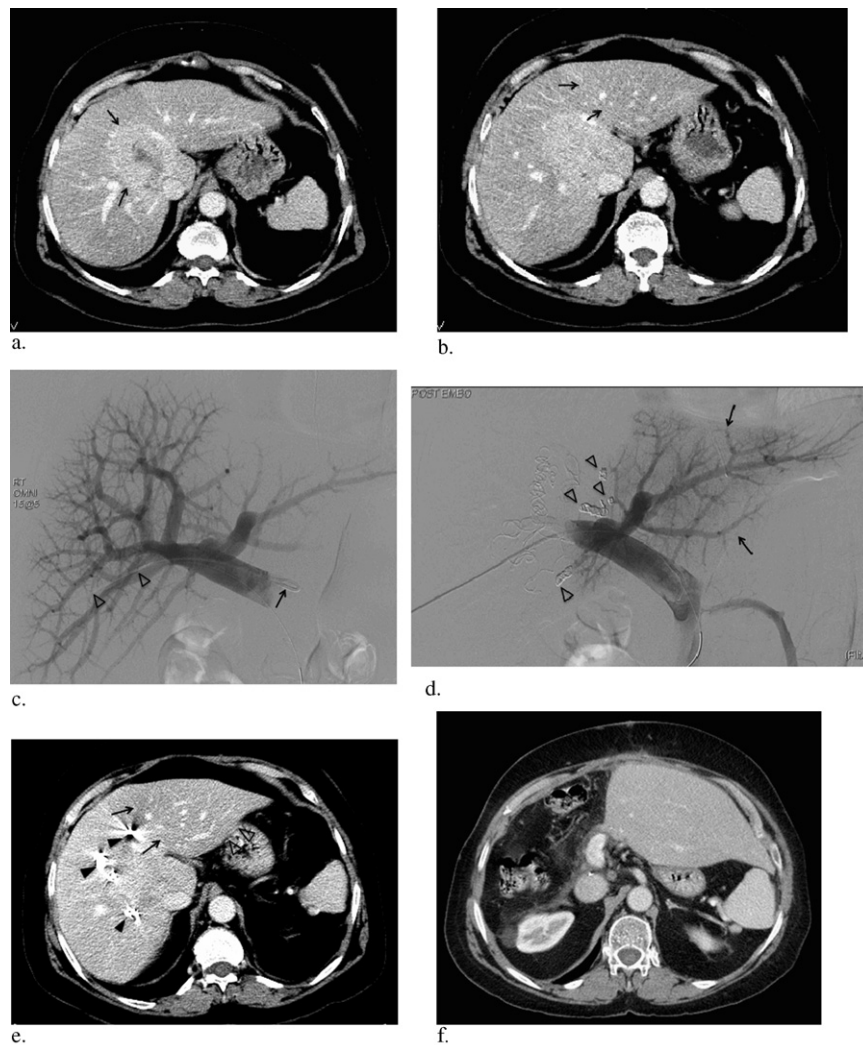


Figure 5. Transhepatic ipsilateral right PVE extended to segment 4 using tris-acryl particles and coils performed in a 74-year-old woman with intrahepatic cholangiocarcinoma. **(a)** Contrast-enhanced CT image of the liver shows a mass (arrows) involving segments 1, 4, 7, and 8 and abutting the inferior vena cava. **(b)** CT image obtained before PVE shows marginal FLR (FLR/TELV = 17%). The FLR is depicted by the arrows. **(c)** Anteroposterior flush portogram shows a 6-F vascular sheath in a right portal vein branch (arrowheads) and a 5-F flush catheter within the main portal vein (arrow). **(d)** Final portogram shows occlusion of the portal vein branches to segments 4–8 with continued patency of the veins supplying the left lateral liver (arrows). Note coils in the segment 4 branches (arrowheads). **(e)** CT image obtained 1 month after right PVE shows substantial FLR hypertrophy (FLR/TELV = 29%). The FLR is depicted by the arrows with newly seen convexity of the left lateral margin (arrowheads). The degree of hypertrophy is 12%. **(f)** CT image obtained after uncomplicated extended right hepatectomy shows massive hypertrophy of the remnant liver.

the FLR has been reported (52,53). Capussotti et al (52) evaluated 26 patients who underwent right PVE ($n = 13$) and combined right and segment 4 PVE ($n = 13$). The authors found no difference in the volume increase ($P = .20$) or rate of increase ($P = .40$) of segments 2 and 3 for right PVE and combined right and segment 4 PVE leading them to recommend against extended embolization. However, more recent studies comparing right PVE and combined right and segment 4 PVE have reported improved hypertrophy of segments 2 and 3 when embolization of segment 4 is also performed (54) without increased incidence of complications (3,54). Kishi et al (54) compared 15 patients who underwent right PVE with 58 patients who underwent combined right and segment 4 PVE. Compared with right PVE alone, the combined right

and segment 4 PVE group demonstrated a greater absolute increase in volume in segments 2 and 3 (median, 106 mL vs 141 mL; $P = .044$) and a higher hypertrophy rate for segments 2 and 3 (median, 26% vs 54%; $P = .021$). The complication rates were similar for right PVE and combined right and segment 4 PVE groups (7% vs 10%; $P > .99$), and no PVE complication precluded resection. It has been suggested that the disparate outcomes between these studies may reflect a difference in technical experience and sample size.

Adjuvant Chemotherapy after PVE

Progression of disease is a primary concern after PVE because it may preclude curative intent surgery. More

recent series on two-stage hepatectomy have reported a 20% dropout rate after first-stage resection because of progression of disease (51,55). In addition, accelerated tumor growth after PVE has been reported for both primary and metastatic liver tumors (56–59). Neoadjuvant chemotherapy can be administered in an attempt to provide tumor control in the interim between PVE and resection; however, concerns have been raised about its potentially deleterious effect on liver hypertrophy and lack of efficacy in preventing progression of disease.

The effects of systemic neoadjuvant chemotherapy on liver hypertrophy after PVE have been addressed by several studies. Zorzi et al (60) reviewed FLR hypertrophy after PVE in patients with colorectal liver metastases who underwent PVE either with concomitant neoadjuvant chemotherapy (n = 43) or without chemotherapy (n = 22) before resection. At 4 weeks, the chemotherapy group, which included 26 patients treated in part with the vascular endothelial growth factor receptor blocker bevacizumab, demonstrated similar rates of hypertrophy compared with the no chemotherapy group.

Similarly, Covey et al (61) reported on patients with colorectal liver metastases who underwent PVE either with neoadjuvant chemotherapy (n = 47) or without chemotherapy (n = 53). These groups showed no significant difference in median contralateral liver growth after PVE. However, a smaller series looking at patients with colorectal metastasis found that patients treated with neoadjuvant chemotherapy after PVE (n = 10) had significantly decreased FLR hypertrophy (median 89 mL vs 135 mL; $P = .016$) compared with patients who did not receive chemotherapy after PVE (n = 5) (62).

Chemotherapy has not been proven to prevent progression of disease between PVE and resection. A more recent study examined the effect of chemotherapy on disease progression between the first and second stages of a two-stage hepatectomy (63). Of the initial 47 patients who underwent first-stage resection, 25 patients (53.2%) were treated with subsequent chemotherapy compared with 22 (46.8%) patients who did not receive interval chemotherapy. Portal vein occlusion was performed in 80.9% of patients (PVE in 27 and PVL in 11), but the relative number of patients in each group treated with PVE or PVL was not reported. Second-stage hepatectomy was not completed in 11 patients (23.4%), all owing to progression of disease. There was no statistically significant difference in either the number of patients with progression of disease or the dropout rates between the groups treated or not treated with interval chemotherapy (progression of disease, 12 vs 13; $P = .561$ and dropout, 16% vs 31.8%; $P = .303$). Conclusions based on these results are tempered by the fact that the decision to treat with interval chemotherapy was made by a disease management team with no randomization. The authors concluded that chemotherapy after first-stage resection does not guarantee lower progression of disease rates.

PVL versus PVE

Intraoperative right PVL has been performed during the initial stage of two-stage hepatectomy or other surgical intervention as a means of inducing FLR hypertrophy without necessitating an additional PVE procedure (64–66). Comparative studies between PVE and PVL have shown mixed results. Aussilhou et al (67) retrospectively compared patients who underwent PVE (n = 18) with patients who underwent PVL during the first stage of a two-stage hepatectomy (n = 17). They found the increase in left liver volume to be similar between the two groups ($35\% \pm 38$ vs $28\% \pm 26$; $P = .7$) and no difference in morbidity (58% for PVE vs 36% for PVL; $P = .6$). Similarly, Capussotti et al (68) retrospectively compared patients with colorectal liver metastases who underwent PVL (n = 17) with patients who underwent PVE (n = 31) at their institution. These authors found similar volumetric increases of segments 2 and 3 for PVE versus PVL (53.4% vs 43.1%; $P = .39$). However, the PVL group had a significantly longer interval between occlusion and CT evaluation compared with the PVE group (median, 40 days vs 29 days; range, 13–135 days vs 18–42 days; $P = .01$).

Other studies found inferior FLR hypertrophy after PVL compared with PVE. Broering et al (69) compared PVL (n = 17) and PVE (n = 17) before extended right hepatectomy for both primary and metastatic disease. Increase in left lateral liver volume was significantly higher for the PVE group compared with the PVL group ($188 \text{ mL} \pm 81$ vs $123 \text{ mL} \pm 58$; $P = .012$). In addition, hospital stay was significantly shorter for PVE compared with PVL (4 days ± 2.9 vs 8.1 days ± 5.1 ; $P < .01$). More recently, Robles et al (70) compared left lobe hypertrophy in patients undergoing two-stage hepatectomy who had PVL (n = 23) versus PVE (n = 18). This group found that PVE resulted in improved median percent increase of the FLR compared with PVL (40% vs 30%; $P < .05$). The inferior hypertrophy after PVL may be explained by portal-portal shunts, which can lead to recanalization of the ligated right portal vein (71). Laparoscopic PVL, although a less morbid procedure than open surgical PVL, has been associated with a 22% rate of inadequate FLR hypertrophy (72).

FUTURE DIRECTIONS

In an attempt to improve on the technical aspects of PVE (eg, better FLR hypertrophy rates, reduced complications), many novel approaches have been developed including transarterial, transsinusoidal, and reversible PVE as well as the addition of stem cell infusion to the FLR after PVE. These approaches are described in this section.

Transarterial PVE

Madoff et al (73) described a technique in pigs of transarterial PVE in which a 3:1 mixture of iodinated oil

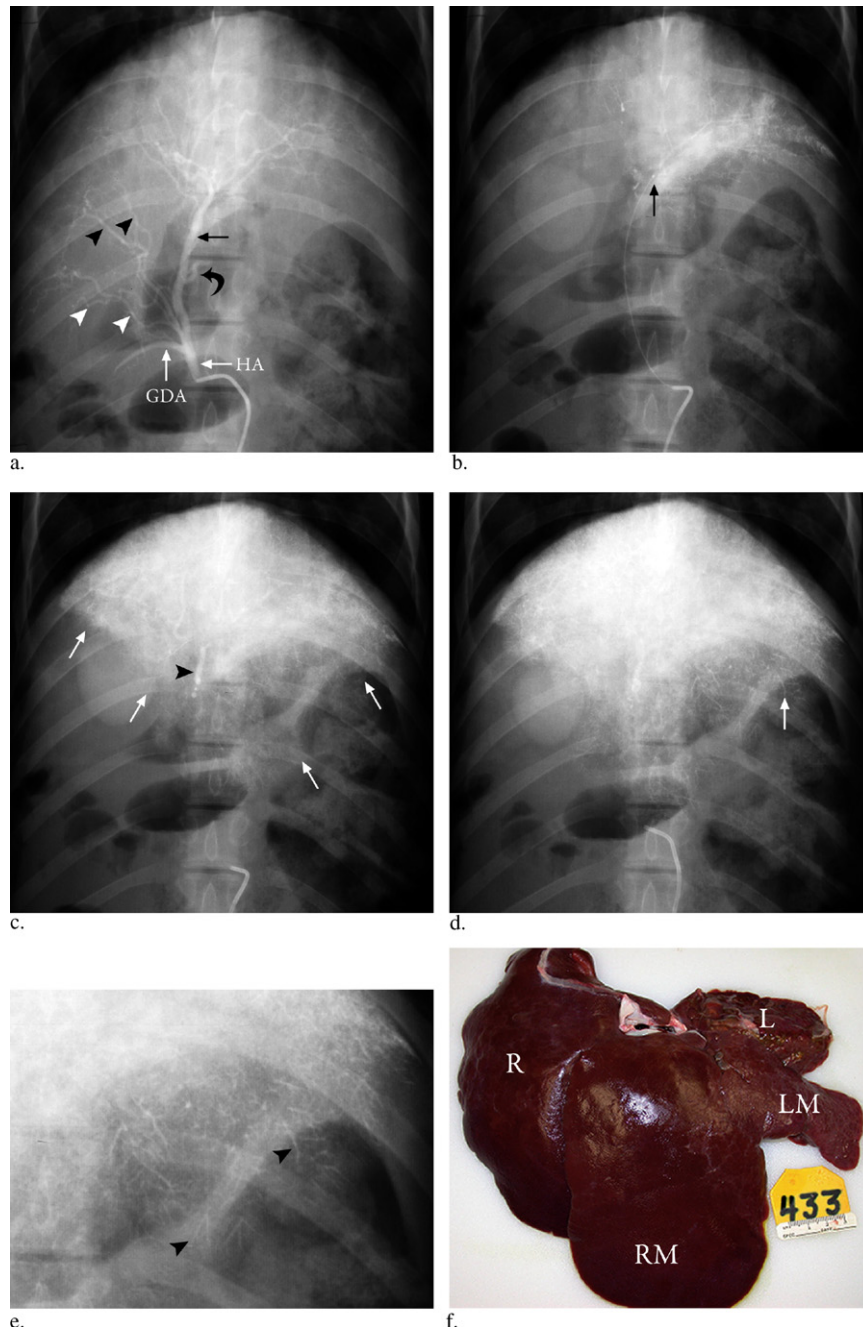


Figure 6. Transarterial PVE procedure. (a) Hepatic anteroposterior arteriogram shows normal hepatic arterial anatomy in a pig. A common trunk (straight arrow) supplies arteries to the left lobe and left middle lobe. The arteries supplying the right lobe (white arrowheads) and the right middle lobe (black arrowheads) are seen. The common hepatic artery (HA), the gastroduodenal artery (GDA), and the right gastric artery (curved arrow) are also shown. (b) Abdominal radiograph shows a 3-F microcatheter (arrow) within the targeted arteries to the left lobe and left middle lobe early within the transarterial PVE procedure. (c) Abdominal radiograph obtained in a later phase of the procedure shows ethiodized oil (Ethiodol)-ethanol mixture within the common arterial trunk (arrowhead) and the dense filling of the mixture within the left lobe and left middle lobe territory (arrows). (d) Abdominal radiograph obtained at completion of the procedure shows filling of many of the small portal branches (arrowheads). (e) Close-up image from (d) shows the Ethiodol-ethanol mixture within the small portal branches (arrowheads). (f) Photograph taken immediately after liver explantation shows massive enlargement of the right (R) and right middle (RM) lobes with severe atrophy of the left middle (LM) and left (L) lobes and part of the right middle lobe that received embolization. The right and right middle lobes have rounded margins, whereas the left and left middle lobes have sharp margins. (Used with permission from Madoff DC, Gupta S, Pillsbury EP, et al. Transarterial versus transhepatic portal vein embolization to induce selective hepatic hypertrophy: a comparative study in swine. *J Vasc Interv Radiol* 2007; 18:79-93.) (Available in color online at www.jvir.org.)

and absolute ethanol was infused slowly through a 3-F microcatheter via lobar hepatic artery branches and allowed to pass into the portal system via the peribiliary

plexus (Fig 6a-f). The investigators performed the procedure in five pigs and compared degree of hypertrophy in five pigs receiving traditional percutaneous transhepatic

PVE. All procedures were technically successful. They found pigs receiving transarterial PVE sustained FLR hypertrophy increases that were nearly double FLR hypertrophy increases sustained by pigs receiving traditional percutaneous PVE. There were no adverse clinical sequelae in the experimental group, and liver function tests were at or near baseline after several days in all animals.

Theoretical advantages described by the authors included a better safety profile than traditional percutaneous transhepatic PVE, which requires direct hepatic puncture. Reported disadvantages of transarterial PVE included longer duration of transarterial PVE procedures necessitated by slow embolic infusion and potential nontarget embolization by virtue of the relatively high incidence of variant hepatic arterial and portal anatomy. Finally, > 19 mL of embolic infusion was required in all transarterial PVE cases, whereas a maximum of 15–20 mL of ethiodized oil has been reported as the upper limit allowable to prevent overt pulmonary complications. The investigators report a limitation of their study being that all animals had normal livers, rather than cirrhotic livers containing tumors. It is uncertain how these factors might alter the flow and effect of the embolic mixture.

Transsinusoidal PVE

Smits et al (74) described a technique in pigs of transjugular or transfemoral retrograde PVE they termed transsinusoidal PVE in which ethylene vinyl alcohol copolymer mixed with tantalum powder in dimethyl sulfoxide (Onyx; ev3, Irvine, California) is injected via a hepatic vein. Because of the low viscosity of Onyx, these investigators were able to reflux the embolic material via the sinusoids into the target portal vein branches by wedging a microcatheter in the selected hepatic vein. The authors correlated transsinusoidal embolization findings with anatomy seen by indirect portography. Potential disadvantages highlighted by the authors included a need to monitor for reflux of the agent toward the base catheter or from venovenous shunting into other hepatic vein branches. In three of eight pigs, embolization of one of two hepatic lobes could not be performed because the investigators could not find a hepatic vein that allowed anatomically appropriate embolization. There was one case of nonocclusive nontarget embolization of the main portal vein secondary to extension of refluxed Onyx from the target portal vein branch. The authors did not measure degree of FLR hypertrophy in this feasibility study.

Reversible PVE

Patients who undergo traditional PVE but do not ultimately undergo resection are typically left with permanently occluded portal veins, which can limit the use of alternative therapies. For this reason, Lainas et al (75) were the first to describe intentional reversible PVE, whereby they found significant FLR volume increases after PVE with absorbable material. Using powdered gelatin sponge

(Curaspon; Curamedical, Zwanenburg, The Netherlands) dissolved in a 4:1 mixture of iodinated contrast medium and saline, the authors reported an average 43% FLR volume increase in nine monkeys at 1 month after PVE, with complete revascularization seen by follow-up direct portography at 12–16 days after the procedure. However, a subsequent rabbit model study found that absorbable gelatin sponge (Gelfoam) resulted in significantly decreased FLR hypertrophy compared with permanent embolic agents (76).

Reversible PVE has also been proposed as a method to improve engraftment of transplanted hepatocytes in the treatment of metabolic liver disease. Dagher et al (77) reported on the results of genetically modified hepatocytes that were autotransplanted into the FLR during reversible partial right PVE in seven monkeys. They documented a 44% mean increase in FLR volume. Biopsies performed 14 days, 8 weeks, and 16 weeks after PVE revealed engraftment of 7.4%, 2.6%, and 1.8% of transplanted cells. These authors concluded that reversible PVE could improve engraftment of transplanted liver cells in the treatment of metabolic liver disease.

PVE with Adjuvant Stem Cell Transplantation

Bone marrow–derived stem cells are known to play a role in liver regeneration and can repopulate damaged hepatocytes (78,79). In 2004, Gehling et al (80) demonstrated that partial hepatectomy induces mobilization of a distinct population of progenitor cells from the bone marrow, identified as CD133⁺, which are capable of differentiation into hepatocytes. Based on these findings, researchers have investigated the intraportal infusion of stem cells in conjunction with PVE to improve rapidity of FLR growth.

Esch et al (81) initially described the use of bone marrow stem cells to improve FLR hypertrophy in 2005; the same group performed a prospective investigation in 2007 (82). In both reports, CD133⁺ stem cells were harvested from the iliac crest at the time of PVE and infused into the FLR shortly after multisegment PVE. The prospective study compared six patients who underwent PVE plus stem cell infusion with seven patients treated with PVE alone. Patients in the PVE plus stem cell group were selected based on clinical concern for inadequate FLR growth. Despite this concern, the PVE plus stem cell group demonstrated a significantly greater increase in mean FLR volume ($P = .049$), greater percent increase of FLR size ($P = .039$), and higher daily growth rates ($P = .03$).

In a follow-up study published in 2012, this same group of investigators reviewed the outcomes of 11 patient treated with PVE plus stem cell with 11 patients treated with PVE alone (83). Both absolute and relative increases in FLR volumes 14 days after PVE were significantly greater in patients receiving PVE plus stem cell than in patients receiving PVE alone. Patients receiving the combined procedure had mean FLR volume growth of

139 mL \pm 66 compared with 63 mL \pm 40 in the PVE only group ($P = .004$). The relative FLR volume increase was also greater for the PVE plus stem cell group compared with PVE alone (10.2% \pm 5.2 vs 4.4% \pm 3.0; $P = .006$). There were no significant differences between groups regarding major complications or 30-day mortality after the procedure. The authors concluded that there is faster FLR growth after PVE combined with stem cell transplantation compared with PVE alone.

CONCLUSIONS

Since the previous review published in this journal, PVE has continued to gain acceptance worldwide as an established procedure to reduce postoperative complications and increase the number of patients able to undergo curative intent surgery. A wealth of outcomes data has proven PVE to be a safe procedure with acceptably low procedure-related morbidity and negligible procedure-related mortality. PVE has also been combined with additional therapies in novel ways to improve its efficacy further. The investigational technique of reversible PVE with transportal stem cell transplant raises hope of transforming traditional PVE for malignant disease into a new, minimally invasive therapy for chronic hepatic insufficiency. Additional research is required to delineate better outcomes-based indications for PVE and to address controversies that continue to arise in the application of this highly successful therapy.

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