Portal Vein Embolization: Rationale, Technique, and Current Application

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Abstract

Portal vein embolization (PVE) is a technique used before hepatic resection to increase the size of liver segments that will remain after surgery. This therapy redirects portal blood to segments of the future liver remnant (FLR), resulting in hypertrophy. PVE is indicated when the FLR is either too small to support essential function or marginal in size and associated with a complicated postoperative course. When appropriately applied, PVE has been shown to reduce postoperative morbidity and increase the number of patients eligible for curative intent resection. PVE is also being combined with other therapies in novel ways to improve surgical outcomes. This article reviews the rationale, technical considerations, and current use of preoperative PVE.

Keywords

- ▶ Portal vein
- ▶ embolization
- ▶ liver resection
- ▶ liver malignancy

Objectives: On completion of this article, the reader will be able to list the indications for portal vein embolization, current technical strategies used in performing the procedure, the expected outcomes, and potential complications.

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Primary liver malignancy has been increasing in incidence over the past several decades, and the liver remains a common site of metastatic recurrence.^{1,2} Surgical resection and liver transplantation are currently the only curative therapies for patients with liver malignancies. Because liver transplantation is limited by donor shortages and strict transplant criteria, liver resection is the mainstay of curative therapy. Improved surgical technique and the liver's unique ability to regenerate allows for the resection of most of the liver, if necessary.³ However, large-volume resections place patients at risk for complications of liver insufficiency, particularly in the perioperative period before the remnant has

increased in volume. Although causes of perioperative liver insufficiency are multifactorial, the percentage of liver that remains after surgery, termed the future liver remnant (FLR), has been shown to be a strong, independent predictor of postsurgical hepatic dysfunction and complications.^{4,5} Preoperative portal vein embolization (PVE) is a safe image-guided procedure that causes hypertrophy of the FLR by redirecting portal blood to the non-tumor-bearing liver. When appropriately applied, PVE has been shown to reduce postoperative morbidity and increase the number of patients eligible for curative intent resection. This article reviews the rationale, technical considerations, and current utilization of preoperative PVE.

Mechanisms of Liver Regeneration

The atrophy-hypertrophy complex refers to the controlled liver regeneration that occurs after hepatocyte injury due to toxicity, vascular occlusion, or trauma. Although termed *hypertrophy*, regeneration occurs mainly from hyperplasia, or an increase in cell number, rather than simply an increase in cell size.⁶ Under normal circumstances, the adult liver is relatively quiescent with a tiny fraction of cells (<0.01%) undergoing mitosis. However, after regional injury, the non-injured liver rapidly undergoes regeneration. The degree of

hyperplasia is proportional to the degree of injury. Small insults result in localized mitotic response; however, injury involving greater than ~10% of liver volume leads to a more generalized response in the remaining liver, with up to 95% of cells undergoing mitosis. In fact, following resection of a two-thirds hepatectomy, the liver can regenerate lost volume within 2 weeks.⁷

Animal models and postresection studies have shown that regeneration is stimulated by growth factors released by the liver, as well as extrahepatic growth factors transported by the portal vein.⁸ The crucial role of the portal vein is evidenced by the fact that the greatest hypertrophy occurs in the periportal zone, with a decreasing gradient toward the hepatic vein.⁹ In addition, Doppler studies have demonstrated that the degree and timing of liver regeneration correlates with the transient increase in portal flow following PVE.¹⁰ Proposed mechanisms of hypertrophy based on animal modeling are multifactorial and include the release of nitrous oxide stimulated by portal pressure changes, release of intrahepatic growth factors and cytokines such as transforming growth factor- α and tumor necrosis factor(TNF)- α , and gut-derived growth factors carried by the portal vein. Hepatocyte growth factor (HGF) plays a central role in liver regeneration. In addition to its direct effects on hepatocyte replication, HGF also stimulates the release of cytokines such as interleukin-6 and TNF- α , which also promote regeneration.¹¹

These mechanisms may explain the diminished or delayed liver regeneration observed in people with diabetes with insulin resistance and patients with cirrhosis. Insulin is known to play an important role in liver regeneration by acting synergistically with HGF and other growth factors.¹² The decreased regenerative capacity observed with cirrhotic livers may result from a poor response to growth factors and diminished portal flow rates. Despite advances in understanding, the details of hypertrophy following PVE are not well understood and inferred largely based on animal models. Observational studies have demonstrated that regeneration after PVE occurs slower than after hepatic resection, possibly due to apoptosis, as opposed to frank necrosis, which occurs after PVE.¹³

Rationale

In 1990, Makuuchi et al published the first report of PVE for the purpose of inducing hypertrophy of nonembolized liver segments before resection.¹⁴ They proposed that PVE could improve surgical outcomes by mitigating the sudden rise in portal pressure that otherwise occurs during surgery, as well as prevent perioperative liver dysfunction by increasing FLR mass. This rationale was confirmed in subsequent studies showing that increased FLR volume is associated with improved biliary excretion, albumin uptake, and postoperative liver function testing.^{15–17}

PVE is a safe procedure that causes few adverse effects and can be performed on an outpatient basis. Most large series report 0% procedure-related mortality.¹⁸ After PVE, half of the patients experience no significant change in liver function tests, and the other half demonstrate small fluctuations that return to baseline after 3 days. Other laboratory values such as

white blood cell count change minimally, if at all, and markers of synthetic function such as albumin levels or prothrombin time are typically unaffected.¹⁹ PVE is also well tolerated by patients. Unlike the postembolization syndrome that occurs after arterial embolization, patients rarely experience nausea, fever, or significant pain. This is attributed to the observation that PVE primarily causes apoptosis rather than ischemic necrosis, thus limiting the release of inflammatory signalers.

Assessment of Future Liver Remnant

Before major hepatectomy, multiphase contrast-enhanced computed tomography (CT) is obtained for preoperative planning and FLR evaluation. The vascular landmarks for hepatic resection are identified, and FLR volume is assessed by CT measurements. This entails outlining the FLR on each axial slice followed by computations based on slice thickness.

The absolute size of the FLR, however, is not sufficient to predict which patients will benefit from PVE. This is because larger patients require a larger liver mass to support essential functions compared with smaller patients. FLR must therefore be standardized relative to patient size as a ratio of FLR to total functional liver volume. Standardized FLR (sFLR), expressed as a percentage of total functioning liver volume, can be compared between patients and surgical outcome data to determine if PVE is indicated.

To calculate sFLR, the entire functioning liver volume must be ascertained. This can also be accomplished by CT volumetric calculations by measuring the entire liver volume and subtracting the volume of tumor within the liver. However, tumor burden is often extensive, making this method tedious and imprecise. In addition, liver tumors that are infiltrative or with indistinct borders can be difficult to measure directly.

Alternatively, total estimated liver volume (TELV) can be calculated using a formula based on the close relationship between body surface area (BSA) and functional liver volume. Vauthey et al developed the following formula by analyzing liver size and body surface area in 292 western adults²⁰

$$\text{TELV} = -794.41 + 1267.28 (\text{BSA}).$$

Although multiple similar formulas exist in the literature, a meta-analysis comparing several variations found the Vauthey formula to be the least biased and most accurate for adult patients.²¹ In addition, this method of calculating sFLR (volumetric FLR/TELV) has been shown to correlate strongly with clinical outcomes.^{5,22}

Patient Selection

Multiple factors are taken into account in deciding which patients would benefit from PVE. These include the extent of liver resection, baseline liver function, and complexity of the planned surgery. PVE is indicated in cases where the FLR is either too small to support essential function or is borderline and associated with a complicated postoperative course.

The indocyanine green (ICG) clearance test was initially designed to study blood flow but has become an important tool for quantifying liver function. ICG is a tricarbo-cyanine dye that binds albumin and distributes in the blood pool shortly after injection. ICG is cleared from the body exclusively via biliary excretion. The degree of excretion can be calculated

either by serum blood test or via an optical sensor placed on the finger. Within 20 minutes of injection, 97% of the dye should be cleared by the liver. For analysis prior to PVE, the ICG-R15 test is typically used. This value describes the percentage of ICG that remains in the blood 15 minutes after injection. Higher ICG-R15 values indicate decreased hepatic reserve and the need for increased FLR.²³

In patients with normal liver function, an FLR as low as 10% can support essential hepatic function.²² However, multiple studies have demonstrated that postoperative complications and length of stay are significantly reduced among patients with sFLR >20%.^{5,22,24} Therefore, for patients with normal livers, PVE is advocated for sFLR <20%.

Liver injury evidenced by hepatic steatosis or exposure to hepatotoxic chemotherapy is also considered in selecting patients for PVE. Hepatic steatosis has been identified as a risk factor for developing postresection surgical complications.²⁵ In one case-control study, patients with hepatic steatosis had significantly higher rates of postoperative hepatic dysfunction, blood transfusions, and stays in the intensive care unit (ICU).²⁶ Retrospective studies have also found a correlation between hepatotoxic chemotherapy regimens and postoperative complications.²⁷ Although no evidence-based cutoffs are currently available, many consider PVE for patients with sFLR <30% and either hepatic steatosis or significant exposure to hepatotoxic chemotherapy.

Many patients with cirrhosis are not considered candidates for major hepatic resection owing to an unacceptable risk of perioperative death. However, a select group with Childs-Pugh class A cirrhosis and preserved liver function (ICG-R15 test <10%) are considered for resection if their sFLR is >40%, below which PVE is indicated.²⁸ This is supported by the only prospective trial comparing PVE before right hepatectomy. This study found decreased postoperative complications, ICU admissions, and length of hospital stay for patients with chronic liver disease who underwent PVE.²⁹ In addition, a 40% cutoff recommendation has been extended to patients with prolonged biliary obstruction.

In addition to the guidelines just discussed, other factors are considered in determining whether any individual patient should undergo PVE. These include patient age, comorbidities such as diabetes, and the complexity of the planned resection such as concomitant partial pancreatectomy. Until evidence-based indications are further defined, the indication for PVE in these patient populations is decided on an individual basis.

Contraindications

The two absolute contraindications to PVE are extensive ipsilateral tumor thrombus and clinically evident portal hypertension. In the setting of extensive ipsilateral tumor thrombus, PVE is contraindicated because most of the portal flow has already been diverted, and safe delivery of embolic agent is difficult.³⁰ Clinically evident portal hypertension is a contraindication to hepatectomy, and therefore PVE is not indicated. PVE in the setting of mild portal hypertension or advanced fibrosis is feasible but considered relatively contraindicated owing to the increased risk of nontarget emboliza-

tion and complications such as bleeding esophageal varices.⁵ Other relative contraindications include uncorrectable coagulopathy and renal insufficiency.

Technical Considerations

The goal of PVE is to achieve complete portal occlusion of targeted segments. Embolizing the entire portal tree including distal branches is important to prevent portoportal shunts. In addition, it is critical to target all diseased segments to maximize hypertrophy of the FLR and prevent hypertrophy of segments planned for resection.

A variety of embolic agents have been described for PVE including n-butyl cyanoacrylate (NBCA) and ethiodized oil, fibrin glue, ethanol, and microparticles such as polyvinyl alcohol or trisacryl gelatin. The ideal embolic agent should be well tolerated by the patient, cause complete occlusion without subsequent recanalization, and be easy to administer. No randomized studies have compared various agents, and retrospective comparisons demonstrate similar efficacy. Each agent carries its own unique technical demands, and selection to date should be guided by operator preference and technical factors relating to catheter approach.

The vast majority of PVE procedures target the right lobe before right hepatectomy (RPVE) or the right lobe plus segment 4 (RPVE + 4) prior to extended right hepatectomy. Left lobe PVE is rarely indicated because the right lobe is asymmetrically larger than the left and typically sufficient in size to support function. Volumetric studies have shown that even with extended left hepatectomy (segments 2, 3, and 4 with extension to the caudate), sFLR is typically >33%. However, extended right hepatectomy typically leaves an sFLR <20%.³¹

PVE can be performed using transileocolic, ipsilateral, or contralateral approaches. The oldest, transileocolic portal vein embolization, is a surgical procedure performed under general anesthesia.³² A right lower quadrant incision is made and a vascular sheath introduced directly into an ileocolic venous branch. A catheter is then advanced under fluoroscopic guidance into the portal vein for subsequent embolization. This avoids direct puncture of the liver, which is particularly advantageous when there is large tumor burden and concern for peritoneal seeding. However, this approach carries the obvious drawbacks of an invasive procedure and general anesthesia. Initial descriptions of PVE used the transileocolic approach, which is still performed by surgeons in Asia and in select cases when a surgical procedure is planned for other purposes. However, most centers with dedicated interventional radiology services prefer transhepatic approaches.

Percutaneous portal vein embolization can be achieved via an ipsilateral approach (through the tumor-bearing liver) or contralateral approach (through the FLR). We describe these techniques with reference to the standard RPVE (► Fig. 1) or RPVE + 4 (► Fig. 2). For either approach, a distal portal branch is accessed under ultrasound guidance. After a vascular sheath is secured, flush portography is performed to assess for variations in portovenous anatomy. In addition, portal pressures are measured throughout the procedure because

Figure 1 Transhepatic ipsilateral right portal vein embolization (PVE) using trisacryl particles and coils performed in a 49-year-old patient with colon cancer metastatic to the liver. (A) Computed tomography (CT) scan obtained prior to PVE shows marginal future liver remnant (FLR) (FLR-to-TEL [total estimated liver volume] ratio: 25%). (B) Anteroposterior flush portogram demonstrates a 6F vascular sheath in a right portal vein branch (arrowheads) and a 5F flush catheter within the main portal vein (arrow). (C) Selective right portogram with use of reverse-curve catheter placed prior to right PVE. (D) Final portogram shows occlusion of the portal vein branches to segments V through VIII with continued patency of the veins supplying the left lateral lobe. (E) CT scan obtained 1 month after right PVE shows substantial FLR hypertrophy (FLR-to-TEL ratio: 50%). The degree of hypertrophy is 25%. (F) CT scan after right hepatectomy demonstrates hypertrophy of remnant liver. (Used with permission from Avritscher R, de Baere T, Murthy R, Deschamps F, Madoff DC. Percutaneous transhepatic portal vein embolization: rationale, technique, and outcomes. *Semin Intervent Radiol* 2008;25(2):132–145.)

significant portal hypertension is a contraindication to hepatic resection.

At our institution, we typically embolize using trisacryl gelatin microspheres (EmboGold Microspheres, Biosphere Medical, Rockland, MA). Smaller particles are infused initially to treat smaller distal branches, with a stepwise increase in microsphere caliber size until near-complete stasis is

achieved. Care is taken to avoid nontarget embolization. Following particulate embolization, 0.035- to 0.038-inch embolization coils (Gianturco, Cook Medical, Bloomington, IN) are placed centrally to prevent recanalization.

We perform the ipsilateral approach when technically feasible. In this approach, the portal venous system is accessed through the tumor-bearing liver (i.e., liver to be

Figure 2 Transhepatic ipsilateral right portal vein embolization (PVE) extended to segment IV using trisacryl particles and coils in a 59-year-old woman with a history of gallbladder carcinoma. (A) Computed tomography (CT) scan obtained prior to PVE shows marginal future liver remnant (FLR) (FLR-to-TLV [total estimated liver volume] ratio: 17%). (B) Anteroposterior flush portogram demonstrates a 6F vascular sheath in a right portal vein branch (arrowheads) and a 5F flush catheter within the main portal vein (arrow). (C) Selective left portogram prior to segment IV embolization shows the veins that supply segments II, III, and IV. (D) Selective portography via a 3F microcatheter (arrowheads) during embolization of segment IVa. (E) Selective left portogram via a 5F catheter (arrow) after segment IV embolization (arrowheads show coils within proximal branches of segment IV). (F) Selective venogram via a 5F reverse-curve catheter with tip in the right portal vein (arrow). Note multiple previously placed coils within segment IV branches (arrowheads). (G) Final portal venogram shows occlusion of the portal vein branches to segments IV through VIII with continued patency of the veins supplying the left lateral lobe. (H) CT scan obtained 1 month after PVE shows substantial atrophy of right liver and segment IV, and FLR hypertrophy (FLR-to-TLV ratio: 26%). The degree of hypertrophy is 9%. The patient underwent successful extended hepatectomy. (Used with permission from Avritscher R, de Baere T, Murthy R, Deschamps F, Madoff DC. Percutaneous transhepatic portal vein embolization: rationale, technique, and outcomes. *Semin Intervent Radiol* 2008;25(2):132–145.)

resected). Anterior branches of the right portal vein are typically targeted because these have been associated with a lower complication rate.³³ For RPVE + 4, we prefer to treat segment 4 first, which avoids the potential difficulty of exchanging catheters through the previously embolized right portal system, as well as the risk of dislodging embolic material during segment 4 embolization. Furthermore, if thrombus or injury inadvertently occurs to the left portal vein during segment 4 embolization, the procedure can be terminated and treatment options reassessed. If the right portal system has already been embolized and nontarget

embolization to the left portal branches occurs, few treatment options remain for the patient. Despite these benefits, some operators choose to embolize the right system first because segment 4 vessels subsequently dilate, making catheterization of segment 4 branches easier.

Embolization of the right hepatic lobe segments via the ipsilateral approach can be technically challenging owing to the acute angles of the segmental branches. For this reason, reverse curve catheters are used to facilitate access. Final portography is performed through the working catheter rather than exchanging for a flush catheter to minimize the

Figure 3 Technique of transhepatic contralateral approach to right portal vein embolization using n-butyl cyanoacrylate mixed with ethiodized oil. (A) Ultrasound view of needle puncture of a segment III portal branch (arrowheads). (B) Anteroposterior flush portogram demonstrates a 5F flush catheter within the main portal vein (arrow). Note portal vein access through the left portal vein (arrowheads). (C) Single image obtained during fluoroscopy shows cast of embolic material (cyanoacrylate and lipiodol) within right portal vein branches (arrowheads). (D) Final portogram shows occlusion of the portal vein branches to segments V through VIII with continued patency of the veins supplying the left lateral lobe. The cast of embolic material is visualized in the treated right portal branches (arrows). (Used with permission from Avritscher R, de Baere T, Murthy R, Deschamps F, Madoff DC. Percutaneous transhepatic portal vein embolization: rationale, technique, and outcomes. *Semin Intervent Radiol* 2008;25(2):132–145.)

risk of dislodging embolic material. The access tract is then embolized to minimize the risk of bleeding at the puncture site.

For the contralateral approach, access is obtained by puncture through the FLR (→**Fig. 3**). Segment 3 branches are commonly targeted because their anterior position allows for easier percutaneous access as well as less acute angles for right portal vein embolization. With this approach, segment 4 is typically embolized following right liver embolization. The contralateral approach has the advantage of easy catheter manipulation to the right lobe segments. In addition, interventions such as biliary drainage in the setting of Klatskin's tumor or thermal ablation of localized disease in the FLR can be achieved at the time of PVE. However, the contralateral approach requires vascular access through the FLR, which can be injured during the procedure.

We prefer the ipsilateral approach because this spares the FLR from the potential damage and associated complication of vascular access. The technical challenge of acute angles can be overcome with the use of reverse curve catheters. The ipsilateral approach does require access through the diseased

liver, which can be problematic in cases of extensive tumor burden. Access through the tumor should be avoided due to the risk of peritoneal seeding. If safe access is not possible, the contralateral approach is a reasonable alternative.

Complications

Complications of percutaneous PVE are similar to other transhepatic procedures. These include subcapsular hematoma, hemobilia, hemoperitoneum, vascular injuries, pneumothorax, and cholangitis. Complications specific to PVE include nontarget embolization, recanalization of embolized segments, and complete portal vein thrombosis. The quality improvement guidelines for PVE published in 2010 by the Cardiovascular and Interventional Radiological Society of Europe assigns an acceptable minor complication rate up to 25% and major complication rate no greater than 5%.³⁴ Abulkhir et al published a meta-analysis in 2008, pooling data from 37 studies with a total of 1088 subjects that included both percutaneous and ileocolic approaches.¹⁸ The overall morbidity was 2.2%, with 0% procedure-related mortality. Similarly low adverse event rates have been published

in other series. Di Stefano et al reported adverse events in 12.8% of patients (24 of 188) who underwent PVE via a contralateral approach.³⁵ Complications in this series included complete portal vein thrombosis ($n = 1$), inadvertent NBCA migration to the left portal vein ($n = 1$), hemobilia ($n = 1$), rupture of metastasis into the gallbladder ($n = 1$), and transient liver failure ($n = 6$).³⁵ Kodama et al reviewed 47 percutaneous PVEs in 46 patients (11 via the contralateral approach).³³ Complications occurred more frequently in the punctured lobe, leading the authors to recommend the ipsilateral approach. Complication rates after PVE appear to be higher in patients with chronic liver disease owing to an increased risk of thrombosis of the nonembolized portal vein.

Outcomes

The degree of hypertrophy expected after PVE differs depending on the degree of underlying liver disease. Patients with otherwise normal livers regenerate at 2 weeks post-procedure at a rate of 12 to 21 cm^3/day , compared with 9 cm^3/day in cirrhotic patients.³⁶ In normal livers, sufficient hypertrophy typically occurs within 2 to 4 weeks, whereas regeneration in patients with cirrhosis can take ≥ 4 weeks.

Cirrhosis is a common comorbidity faced because hepatocellular carcinoma (HCC) frequently develops in the setting of advanced liver disease. Although most patients with cirrhosis do not meet resection criteria, those who are considered for resection require a relatively robust sFLR ($>40\%$) to lower their acceptable risk of postoperative liver insufficiency and mortality. PVE has been shown successful in increasing the number of cirrhotic patients eligible for surgery and concomitantly improving perioperative outcome. Azoulay et al performed PVE on 10 patients with HCC and cirrhosis who had a sFLR $<40\%$.³⁷ In this study, PVE resulted in hypertrophy and allowing for subsequent resection in all 10 patients. The PVE group's overall and disease-free survival was similar to the 19 patients who did not undergo PVE. Palavecino et al published retrospective data of 54 patients with HCC, 21 of whom received PVE before hepatectomy involving at least three segments.³⁸ There were no perioperative deaths in the PVE group compared with six perioperative deaths (18%) in the non-PVE group ($p = 0.038$). Excluding perioperative deaths, overall and disease-free survival rates were similar between the two groups.

In patients with normal liver function, PVE is indicated when sFLR is $<20\%$, as is often the case before extended right hepatectomy. Multiple studies have demonstrated improved outcomes in patients with normal liver function undergoing RPVE + 4. A large published series of 301 consecutive patients who underwent extended right hepatectomy found that mortality and postoperative liver insufficiency rates were significantly higher in patients with FLR $<20\%$ ($p < 0.05$), but no difference was demonstrated between patients with FLR between 20% and 30% and patients $>30\%$.²⁴

Sequential Arterial and Portal Embolization

Transcatheter arterial chemoembolization (TACE) is commonly used to provide locoregional control of unresectable

HCC, as well as being performed as a bridge to transplant.³⁹ In addition, interest has developed in applying this therapy in sequence with PVE prior to hepatectomy for HCC. There are several theoretical benefits of this combination therapy. As discussed earlier, cirrhotic livers demonstrate a decreased propensity to regenerate and often require longer time intervals to achieve satisfactory hypertrophy. Necrosis, as occurs after TACE, typically leads to increased rates of liver regeneration. In addition, HCC, which often arises in the setting of cirrhosis, derives its blood supply preferentially from the hepatic artery. After PVE, hepatic arterial flow within the embolized segment increases (termed the *hepatic artery buffer response*), which can lead to an accelerated growth of tumors.⁴⁰ TACE may therefore provide local control of tumors during the interval between PVE and resection. Finally, HCC is associated with the formation of arteriportal shunts that can attenuate the effects of PVE, which is typically performed upstream from the shunts.⁴¹ These arteriportal shunts are also targeted during TACE.

Ogata et al published an analysis of 36 patients with HCC and cirrhosis who underwent resection after PVE; 18 of these patients (50%) had TACE 3 weeks prior to PVE.⁴² The mean increase in FLR volume was higher for the TACE plus PVE group compared with PVE alone (12.5% versus 8.4%; $p = 0.022$). The TACE plus PVE group also had a significantly increased incidence of complete tumor necrosis (15 of 18 vs 1 of 18; $p < 0.001$) and a statistically significant higher 5-year disease-free survival (37% versus 19%; $p = 0.041$).

More recently, Yoo et al reported their results of 135 patients with HCC, 71 of whom underwent TACE plus PVE and 64 who underwent PVE only (prior to right hepatectomy).⁴³ In this series, PVE was performed an average of 1.2 months after TACE. The TACE plus PVE group had a higher mean increase in sFLR (7.3% versus 5.8%; $p = 0.035$), as well as improved overall ($p = 0.028$) and recurrence-free ($p = 0.001$) survival.

Portal Vein Embolization and Two-Stage Hepatectomy

Two-stage hepatectomy was developed as a means of providing potentially curative therapy to patients with colorectal metastases confined to both lobes of the liver. Using traditional criteria, this pattern of disease was previously considered unresectable. However, a two-stage surgical approach, often using hypertrophy following PVE, can provide a curative option to carefully selected patients. During the first stage of hepatectomy, tumor within the FLR is resected or, in some cases, ablated. Once the FLR is devoid of tumor, PVE can be performed to increase its mass. PVE is often necessary because these patients typically receive hepatotoxic neo-adjuvant chemotherapy, and therefore a FLR $>30\%$ is preferred. After PVE, a right or extended right hepatectomy can be safely performed.

Narita et al reported on the outcome of 61 patients who completed two-stage hepatectomy, all but 3 of whom incorporated PVE or ligation.⁴⁴ The 5-year overall survival was 32%, and overall median survival was 39.6 months. In a separate study, Brouquet et al reported outcomes of 65 patients who underwent first-stage hepatectomy and 47 who completed

the two-stage hepatectomy.⁴⁵ The overall 5-year survival rate was 51% for the group and 64% for the 47 patients who completed the second-stage resection.

Future Directions

Stem cell infusion in conjunction with PVE has gained interest as a means of promoting the rate and degree of FLR hypertrophy. In animal models, hematopoietic stem cells from the bone marrow have been shown to enter the liver via the portal vein and participate in regeneration.⁴⁶ This finding is corroborated in humans; liver biopsies from patients who had undergone allogeneic stem cell transplant demonstrated donor DNA within regenerated hepatocytes.^{47,48} Researchers have subsequently investigated the infusion of hematopoietic stem cells into the FLR during PVE. One recent study reports on the portal infusion of CD133+ bone marrow derived stem cells (SC) in conjunction with PVE.⁴⁹ PVE with portal infusion of CD133+ stem cells (PVE plus SC) was performed on 11 patients, and results were compared with 11 patients who underwent PVE only as well as 18 controls. At 14-days posttreatment, FLR growth was significantly higher for the PVE plus SC group compared with PVE only (138.66 cm³ versus 62.95 cm³, respectively; $p = 0.004$). Future studies are needed to assess whether SC infusion has an impact on surgical outcomes and survival.

Other areas of ongoing research include the development of new embolic agents, new percutaneous approaches, and the development of better defined criteria for patient selection.^{50,51}

Conclusion

PVE continues to play an important role in the surgical management of liver malignancy, allowing for more aggressive resections and safer postoperative courses. Future research and experience will no doubt drive ongoing refinement of the technique going forward.

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