Gastrointestinal Intervention

Review Article

Portal vein embolization prior to hepatectomy: Techniques, outcomes and novel therapeutic approaches

Matthew L. Hung,* Justin P. McWilliams

A B S T R A C T

Hepatectomy plays a pivotal role in the management of primary and secondary malignancies of the liver, and offers a curative option for the patient. Postoperative liver failure is a severe complication of liver resection, particularly for patients with underlying liver disease. Portal vein embolization (PVE) is a well-established preoperative technique that redirects blood flow to the anticipated remaining liver after resection in an effort to improve the functional hepatic reserve. PVE has improved the safety of hepatectomy and has extended surgical candidacy to patients who previously would have been ineligible for resection because of insufficient remnant liver volume. This article reviews the following aspects of PVE; indications, contraindications, liver volumetry, approaches, embolization agents, recent outcomes data, and areas of active research including adjunctive therapies and temporary PVE.

Copyright © 2018, Society of Gastrointestinal Intervention. All rights reserved.

Introduction

Despite advancements in systemic and locoregional therapies over recent years, liver resection has maintained a vital role in the treatment algorithm of both primary and metastatic liver tumors.[1,2] A key determinant to the safety of liver resection is the remaining liver volume following surgery, known as the future liver remnant (FLR). Multiple studies have demonstrated that the FLR predicts the risk of post-hepatectomy liver failure and mortality.[3–5] Several strategies have been developed to induce growth of the FLR and therefore increase resectability. These include portal vein embolization (PVE), associating liver partition and portal vein ligation, and transhepatic liver venous deprivation (LVD).[6–8]

PVE is the most commonly utilized technique to promote growth of the FLR prior to hepatectomy. The aim of PVE is to redirect the flow of portal blood, thereby inducing atrophy in the diseased liver segments to be resected, and compensatory hypertrophy in the non-embolized liver segments which will become the FLR. PVE has been shown to reduce the morbidity of major hepatectomy and has extended surgical candidacy to patients who otherwise would have had insufficient liver volume precluding

resection.[9–11] In this article, we review the indications and contraindications for PVE, liver volumetry, technical considerations, and recent outcomes for PVE alone and in combination with other techniques.

Indications and Contraindications

Patients are candidates for PVE if they have primary or metastatic liver tumors eligible for resection and have an estimated FLR volume that is not large enough for adequate function in the perioperative period.

Severe portal hypertension precluding surgery, manifested by a hepatic venous pressure gradient > 12 mmHg, refractory ascites, or variceal bleeding, is considered an absolute contraindication to PVE.[12] Patients with metastatic disease or periportal lymphadenopathy are ineligible for resection and therefore would not benefit from PVE. Although two-stage hepatectomy has extended surgical candidacy to patients with bilobar disease,[13] diffuse multifocal disease remains a contraindication to PVE. PVE is unnecessary in the case of complete lobar portal vein thrombosis, as flow is already diverted.[14] Other relative contraindications include

uncorrectable coagulopathy, renal failure, and uncorrectable biliary dilatation in the FLR.

FLR Measurement and Threshold Determinants

Overestimation of the FLR may mislead the medical team into thinking that a given patient may proceed to resection safely, which could put the patient at risk for post-resection liver failure. In the case of underestimation, a patient may have sufficient FLR for resection, but could undergo unnecessary PVE, which would delay surgery and put the patient at risk for further complications. Thus, it is important to consider the methodology used to measure or estimate the FLR and liver function, and the clinical factors that influence the volume of FLR necessary to minimize the risk of post-resection liver failure.

In addition to the FLR, the total estimated liver volume (TELV) must also be calculated, as there is a linear correlation between liver volume and body size.[15,16] The normalization of the FLR by TELV is known as the standardized FLR (sFLR), and it is this percentage that is most often used clinically. Computed tomography (CT) volumetry is an established method used to measure liver volumes, and has an error rate < 5%.[17] However, this assessment requires delineation of the total liver volume, FLR volume and tumor volume. Although new software is being developed to allow for auto-segmentation, standard techniques for CT volumetry are time-consuming.[18,19] An alternative method developed by Vauthey et al[20] uses a formula based upon the patient's body surface area (BSA) to estimate liver volume: TELV = −794.41 + 1,267.28 × BSA. The literature has produced conflicting results with regards to the superiority of one method over the other. Ribero et al[21] found that CT volumetry underestimated the risk of hepatic insufficiency in 11% of patients. In contrast, Leung et al[22] found that measured volumetrics correlated with outcomes better than estimated volumetrics. A recent study by Martel et al[23] demonstrated poor concordance between the two methods, with a difference in the FLR of ≥ 5% in almost one-third of patients. Some groups have[24,25] developed formulas to estimate total liver volume without using body weight-related variables, in consideration of the artificial effects that ascites and edema have on body weight. Although these new formulas predicted total liver volume more accurately than standard formulas within certain patient cohorts, they lack multi-center validation.

The volume of liver remnant necessary for adequate hepatic function depends on a number of clinical factors. The presence of underlying cirrhosis is the most important consideration. Compared to a fibrotic liver, normal hepatic parenchyma has better synthetic function and is more likely to undergo the hypertrophy necessary for FLR augmentation. In general, the minimum sFLR required to be considered a hepatectomy candidate is 20% for a patient with a normal liver and 40% for a patient with evidence of cirrhosis.[26,27] The patient's medical comorbidities and chemotherapy regimen must also be considered. Patients with diabetes mellitus demonstrate reduced and delayed FLR hypertrophy compared to normoglycemic patients,[28] as insulin is a mitogenic factor that works in concert with hepatocyte growth factor (HGF). Oxaliplatin and irinotecan, components of the FOLFOX and FOLFIRI chemotherapeutic regimens commonly used for colorectal cancer, have been shown to induce steatohepatitis and increase 90-day mortality after resection compared to patients without steatohepatitis (14.7% vs 1.6%).[29] In light of these findings, Shindoh et al[30] identified an FLR threshold of 30%, above which the risk of postoperative hepatic insufficiency was reduced in patients with > 12 weeks of preoperative chemotherapy. Lastly, the extent of resection must be considered because a larger hepatic reserve may be required to reduce postoperative morbidity in complex surgeries (e.g., hepatectomy with pancreaticoduodenectomy).

Rather than relying on liver volumetrics as a proxy, some groups investigated the utility of measuring dynamic hepatic function, most commonly through the indocyanine green (ICG) clearance test.[31–33] ICG is a non-toxic dye that binds to plasma proteins and is exclusively removed by the liver. Poor clearance of ICG is predictive of liver failure following resection.[34] Mihara et al[35] developed a formula incorporating both the ICG plasma clearance rate and sFLR that predicted postoperative liver failure in a retrospective analysis of 172 patients. Some guidelines consider the ICG retention rate at 15 minutes when determining FLR thresholds.[36]

Technical Considerations

Approaches

The goal of PVE is to ensure that the entire portal system within the liver to be resected is completely embolized while maintaining the integrity of the FLR. Partial embolization may result in residual portal flow, the formation of collaterals, and potentially reduces the stimulus for compensatory hypertrophy. There are a variety of approaches to access the portal venous system.

One of the earliest techniques was the transileocolic approach,[37] which involves a laparotomy and direct cannulation of the ileocolic vein in order to advance a balloon catheter to the portal venous system. However, as minimally invasive techniques have improved, the transileocolic approach has fallen out of favor. It is now reserved for rare circumstances in which a percutaneous approach is considered high-risk (e.g., presence of multiple large tumors that present risk of peritoneal seeding if punctured), or if the patient requires additional embolization during the same surgical exploration.[38]

The most commonly performed technique today is transhepatic portal access. If the point of entry is in the FLR, it is called a transhepatic contralateral approach,[39] while access of a portal vein branch within the diseased liver to be resected is considered an ipsilateral approach.[40,41] Each approach has distinct advantages and disadvantages, with the decision often depending on operator experience and preference, as well as the embolic material used.

In the contralateral approach, the catheter travels from the left portal system to right portal vein branches, resulting in a more linearized pathway which makes the procedure technically easier. Because the embolic material is delivered in an antegrade fashion in the contralateral approach, there is reduced risk of dislodging the material during catheter manipulation or portography. Furthermore, there is a lower chance of catheter entrapment when using N-butyl cyanoacrylate (NBCA). The main disadvantage of the contralateral approach is potential damage to the FLR parenchyma and the left portal vein. Care must be taken to reduce the number of hepatic punctures and to gently manipulate the catheter to avoid vessel trauma.

The main advantage of the ipsilateral approach is that it avoids trauma to the FLR. It also provides easy access to segment 4 for embolization when two stage or extended right hepatectomy is planned. Access tract embolization can be performed with the ipsilateral approach to reduce the risk of perihepatic hemorrhage, but is often avoided in the contralateral approach due to the risk of nontarget embolization. Despite these advantages, the ipsilateral approach is technically challenging due to the acute angula-

tions between the right portal vein branches, which require either a reverse-curved catheter or an occlusion balloon catheter with multiple lumens for access and embolization. Compared to the contralateral approach, there is also an increased risk of dislodging the embolic material during portography or catheter manipulation, which could potentially damage the FLR.

The technical success of each approach is near 100%, and complication rates are similar. Di Stefano et al[42] found an adverse event rate of 12.8% in a series of 188 patients who underwent PVE with a contralateral approach. Ribero et al[43] analyzed a series of 112 patients who underwent PVE with an ipsilateral approach and found an 8.9% adverse event rate. Kodama et al[44] provided a direct comparison of the complication rates for each approach. There was an 18.1% complication rate in the group of patients who underwent contralateral PVE, and a 13.9% complication rate for patients who underwent ipsilateral PVE. Although this difference was not statistically significant, the authors recommended an ipsilateral approach to reduce the risk of injury to the FLR.

The use of a transsplenic approach was recently reported by Sarwar et al[45] and Ko et al.[46] This approach does not require maneuvering around the acute angulations of the right portal system, avoids the potential for tumor seeding as encountered in the ipsilateral approach, and does not violate the FLR as required by the contralateral approach. The main drawback is the potential for bleeding complications due to the spleen's high vascularity. In the larger series of 27 transsplenic PVEs, the technical success rate was 88.9%, with 2 cases of failed splenic vein puncture and 1 case of splenic vein dissection. The complication rate was 11.1%. Although there were no overt bleeding complications in either report, 1 patient accumulated a small fluid collection in the splenic hilar area. Importantly, 92% of patients underwent planned liver resection.

Embolic agents

A broad spectrum of embolic agents has been used in PVE, including NBCA, gelatin sponge, polyvinyl alcohol (PVA) particles, fibrin glue, absolute ethanol, sodium tetradecyl sulfate foam, or combinations of these materials with coils or vascular plugs.[47–54] Outcomes with respect to the choice of embolic agent will be discussed later, although there is no consensus on the ideal material.

NBCA is a water insoluble liquid that rapidly polymerizes upon contact with blood. It is mixed with lipiodol to confer radiopacity and to titrate the speed of polymerization; dilution with lipiodol slows polymerization, which is favorable for embolization of distal portal branches. NBCA causes significant periportal inflammation and produces durable portal occlusion.[55] However, there is a learning curve to the delivery of NBCA, and each PVE approach presents unique challenges. An ipsilateral approach utilizing a reverse-curved catheter risks catheter entrapment, while a contralateral approach requires manipulation through the FLR. Proper titration of NBCA with lipiodol is necessary to avoid non-target embolization.

Absolute ethanol is a sclerosant that is caustic to vascular endothelium and has been shown to produce durable portal occlusion.[56] However, it has cytotoxic effects on the surrounding hepatic parenchyma, and must be delivered via contralateral approach with an occlusion balloon catheter to prevent nontarget damage. It may also have systemic effects such as intoxication and abdominal pain, which could lead to poor patient tolerance.

Particulate formulations with PVA or gelatin sponge are able to mechanically obstruct distal branches and induce clot formation and thrombosis. Particle embolization can be performed with

an ipsilateral approach and standard catheters.

Fibrin glue consists of a mixture of fibrinogen and thrombin, the final components of the normal coagulation cascade. Iodized oil is added to the mixture to confer radiopacity. The disadvantage with this approach is the necessity of a multi-lumen balloon occlusion catheter,[57] which is not widely available.

Coils and vascular plugs have been shown to be useful as an adjunct to particle embolization.[58] However, the use of these materials alone typically does not produce adequate FLR hypertrophy because they do not achieve sufficient distal embolization.

Outcomes

Complications

Minor complications of PVE include abdominal pain, fever and nausea.[36] Major complications are similar to those encountered in other transhepatic procedures, and include liver abscess, cholangitis and sepsis, subcapsular hematoma, arterioportal fistula, and pneumothorax.[36] Complications specific to PVE include non-target embolization, extension of or de novo portal vein thrombosis, and recanalization of embolized portal vein segments. The overall complication rate ranges from 0.1% to 14.9%, with no mortality reported in one meta-analysis of 1,088 patients.[9,44,59] However, a recent report by Huisman et al[60] suggests that complication rates may be higher in patients who underwent PVE but did not undergo subsequent resection. In this series, 31% of patients who only underwent PVE developed liver abscesses, compared to 8% of unresectable patients who did not undergo PVE.

Hypertrophy response

Compensatory hypertrophy is maximal during the first 3 weeks following PVE.[43] Most studies report the hypertrophy response as a percentage volume increase in the FLR, defined as: $(FLR_{post-PVE} - FLR_{pre-PVE}) / FLR_{pre-PVE} \times 100\%$. A systematic review by van Lienden et al[59] reports an overall mean percentage increase in the FLR of 37.9%. A comparison of hypertrophy response by PVE technique is provided in Table 1. Cirrhotic patients experience a blunted hypertrophy response with a FLR percentage volume increase that is 7.6% to 17.2% lower than that of non-cirrhotic pa-

Table 1 Comparison of Hypertrophy Response by Technique

Technique	No. of patients	Increase in FLR (%)
PVE alone		
PVA + coils/vascular plug[54,58]	77	44.0–53.3
Gelatin sponge[49]	84	30.7
N-butyl cyanoacrylate[52,53]	253	41.7–57.8
Fibrin glue[50]	105	27.4
Sodium tetradecyl sulfate foam[51]	35	48.8
Sequential TACE and PVE[76]	71	21.4
PVE with stem cells[81]	20	33.0
PVE with branched-chain amino acids[85]	13	32.1
PVE and HVE[89]	10	53.4
Reversible PVE[94]	20	29.4

PVE, portal vein embolization; PVA, polyvinyl alcohol; TACE, transarterial chemoembolization; HVE, hepatic vein embolization; FLR, future liver remnant.

tients.[6,61] A recent study by Yamashita et al[62] of 319 patients with hepatocellular carcinoma, biliary tract cancer, or colorectal liver metastases demonstrated that the degree of hypertrophy did not significantly differ by cancer type. Although chemotherapy has been shown to induce steatohepatitis, it does not appear to affect the hypertrophy response in several series.[63,64] There is a highly variable individual response to PVE, even after dichotomizing patients based on the presence of cirrhosis. A recent study by Zeile et al[65] examined cofactors influencing the hypertrophy response in a cohort of 28 patients. They found the formation of new portoportal collaterals following PVE and low plasma total protein levels to be predictive of an sFLR percentage volume increase < 25%. These findings emphasize the importance of complete embolization to prevent the formation of collaterals, while a low protein level may be due to a higher degree of fibrosis or a reflection of the patient's nutritional status.

Comparative studies between embolic materials are limited, although a few trends have emerged. Geisel et al[58] demonstrated that the percentage volume gain in FLR was significant higher in patients who underwent particle embolization with additional central plug and/or coil embolization compared to patients who underwent particle embolization alone (53.3% vs 30.9%). The reported sFLR percentage increase trends higher in studies utilizing NBCA.[59] Comparative studies by Guiu et al[66] (NBCA vs Bead Block plus coils) and Jaberi et al[67] (NBCA plus central plug vs PVA particles ± coils) indicate a superior hypertrophy response with NBCA. However, Jaberi et al[67] found that the choice of embolic agent did not lead to differences in surgical candidacy, outcomes or complications.

Surgical and oncologic outcomes

Recent systematic reviews indicate that 70% to 80% of patients proceed to liver resection following PVE.[59,68] The most common reasons for cancelling resection were either intrahepatic tumor progression or extrahepatic tumor spread. Other causes include insufficient hypertrophy of the FLR, complications of PVE leading to nonresectability, and preoperative mortality. For patients who undergo liver resection following PVE, the rate of posthepatectomy liver failure is 10%.[68] The patient's preoperative status significantly affects the risk of postoperative liver insufficiency. In a recent analysis by Olthof et al,[69] there was a postoperative liver failure incidence of 24% in a series of 217 patients with perihilar cholangiocarcinoma. Multivariate logistic regression revealed jaundice at presentation, an immediate preoperative bilirubin > 2.9 mg/dL and preoperative cholangitis as significant predictors of liver failure.

Previous reports have raised concerns about PVE stimulating tumor growth.[70,71] However, recent evidence suggests that this does not appear to affect oncologic outcomes. Giglio et al[72] compared the outcomes of 668 patients undergoing major liver resection with or without PVE. No significant differences were observed in postoperative hepatic recurrence, 3-year overall survival (OS) or 5-year OS. Similarly, Huiskens et al[73] compared propensity score-matched cohorts and found that PVE does not significantly impact 3-year disease-free survival or 5-year OS for patients undergoing major liver resection for colorectal liver metastases. Another propensity score-matched analysis performed by Beppu et al[74] found that extrahepatic recurrences were less common in patients who underwent PVE compared to those who did not (18.1% vs 38.8%).

Adjunctive Therapies

Sequential TACE and PVE

Another strategy to further induce FLR hypertrophy combines a commonly used interventional technique, transarterial chemoembolization (TACE), with PVE.[75–77] The occlusion of arterial flow increases the stimulus for compensatory hypertrophy, potentially limits the development of arterioportal shunts which may hinder the effectiveness of PVE, and provides an anti-tumor effect. Yoo et al[76] studied 71 patients who underwent sequential TACE and PVE and 64 patients who underwent PVE alone. Patients who received both treatments benefited from increased FLR hypertrophy, decreased incidence of postoperative liver failure (4% vs 12%), and higher OS in a 10-year follow-up period. Ogata et al[75] found a higher incidence of complete tumor necrosis (83% vs 6%) and 5-year disease-free survival rate (37% vs 19%) in patients who underwent sequential TACE and PVE compared to patients who underwent PVE alone. Although the incidence of liver failure does not appear to be higher with this combined approach, it is important to stage the procedures at least 2 to 3 weeks apart to allow liver function tests to normalize, because there is significant segmental infarction even within noncancerous liver after TACE.[78]

PVE with delivery of stem cells

Several clinical studies have demonstrated encouraging results in augmenting the hypertrophy response by infusing hematopoietic stem cells (HSCs) into the portal vein branches of the FLR at the time of PVE.[79–81] The underlying mechanism is unclear, but HSCs may support the generation and activation of oval cells, which are hepatic progenitor cells that can differentiate into hepatocytes.[82] Esch et al[79] compared 22 patients who underwent PVE in combination with simultaneous administration of CD133^{+} bone marrow stem cells versus PVE alone. In this study, patients who received the stem cell infusion demonstrated increased growth of the FLR after 2 weeks compared to patients who underwent PVE alone (138.66 mL vs 62.95 mL). A recent study by Ludvík et al[81] evaluated the FLR hypertrophy response of 40 patients who underwent PVE with or without the application of HSCs. Once again, the growth response at 3 weeks was more robust in patients who received HSCs (173.2 mL vs 98.9 mL). Regardless of whether stem cell infusion was performed, the patients in this study did not differ significantly with respect to the progression of metastases. However, an increase in the total volume of metastases after PVE was found in nearly all patients after administration of HSCs. More studies reporting oncologic outcomes are needed before this adjunctive technique is widely adopted.

PVE with biomolecules

A variety of organic compounds, including branched-chain amino acids (BCAAs) and bile acids, have been shown to stimulate HGF production and promote liver regeneration.[83,84] A randomized trial conducted by Beppu et al[85] studied patients who were given a conventional diet with ($n = 13$) or without ($n = 15$) BCAA granules. Dietary supplementation was provided before PVE and continued for 6 months following hepatectomy. Quantitative functional liver volume was evaluated using ^{99m}Tc-galactosyl human serum albumin scintigraphy. The patients who received BCAA granules demonstrated significantly increased liver uptake value in comparison to patients who had a conventional diet alone (266.7% vs 77.6%). A recent preclinical study by Olthof et al[86] al-

located rabbits who underwent PVE to receive obeticholic acid (a bile acid analogue) or vehicle in the peri-procedural period. FLR hypertrophy was significantly greater in animals who received obeticholic acid (56.1% vs 26.1%). The effects of infusing HGF itself has also been studied by Mangieri et al,[87] utilizing rodents who underwent portal branch ligation, a procedure equivalent to PVE in humans. Rodents who received perioperative HGF infusions demonstrated increased degree of hypertrophy (159.23% vs 47.11%) compared to rodents who underwent portal branch ligation alone. More translational studies are needed to see if any of these biomolecules can prove as a useful clinical adjunct to PVE in humans.

PVE with HVE

A potential limiting factor in the efficacy of PVE is compensatory arterial hyperperfusion in the embolized lobe. Ipsilateral arterial embolization has been explored, but was found to strongly increase the risk of liver abscess due to ischemia.[88] Hepatic vein embolization (HVE) is a reasonable alternative that causes outflow obstruction, thereby attenuating arterial hyperperfusion and inducing further damage to the embolized liver lobe without total ischemia. Combined PVE and HVE, known as biembolization or LVD, has shown promise in limited studies.[8,89,90] A study by Guiu et al[89] of 10 patients who underwent biembolization demonstrated a mean FLR volume increase of 53.4%, with 90% of patients proceeding to resection and no reports of post-hepatectomy liver failure. Le Roy et al[90] reported a mean FLR volume increase of 52.6% in 7 patients who underwent biembolization. Six patients in this cohort proceeded to resection without postoperative liver failure. Although these results are encouraging, both of these studies lacked a comparison arm.

Temporary PVE

While the majority of interventionalists perform PVE with permanent materials such as NBCA, temporary or reversible PVE with absorbable materials offers distinct advantages and could be appropriate in certain clinical niches. First, the use of an absorbable agent could decrease the risk of definitive nontarget embolization to the FLR. Second, a substantial number of planned resections are canceled due to tumor progression. In these patients, the permanently embolized liver segments are prone to complications such as abscesses, and reversible PVE would theoretically be safer. Third, reversible PVE can be repeated, which presents yet another strategy for boosting the hypertrophy response.[91] Finally, reversible PVE could potentially be applied in living-related liver transplantation to increase graft volume before procurement. Recent preclinical studies in mice and rabbits demonstrate that temporary PVE induces hypertrophy of contralateral liver lobes comparable to that achieved with permanent embolization.[92,93] Furthermore, regenerative and functional capacities of the liver appear to be preserved following portal vein recanalization. Tranchart et al[94] studied 20 patients who underwent temporary PVE with absorbable gelatin sponge powder. Although the median FLR hypertrophy response of 29.4% in their study is lower than that of several series that use permanent embolization agents, all patients (n = 20) in the study cohort experienced sufficient hypertrophy to permit surgical planning.

Conclusions

PVE is a well-established technique that has improved the safety of liver resection and has extended surgical candidacy to many patients with primary and secondary liver tumors. A number of technical approaches and embolic agents are available to the interventionalist. In most cases, adequate hypertrophy of the FLR can be achieved with low morbidity. However, tumor progression or insufficient FLR volume may preclude surgery in 20% to 30% of cases. A variety of adjunctive techniques have been recently studied and show great promise in augmenting the hypertrophy response. Reversible PVE is another exciting area of future research and could potentially expand the indications for PVE.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Orcutt ST, Anaya DA. Liver resection and surgical strategies for management of primary liver cancer. *Cancer Control.* 2018;25:1073274817744621.
2. de Ridder JA, Lemmens VE, Overbeek LI, Nagtegaal ID, de Wilt JH; Dutch Liver Surgery Group. Liver resection for metastatic disease; a population-based analysis of trends. *Dig Surg.* 2016;33:104–13.
3. Shoup M, Gonen M, D'Angelica M, Jarnagin WR, DeMatteo RP, Schwartz LH, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. *J Gastrointest Surg.* 2003;7:325–30.
4. Shirabe K, Shimada M, Gion T, Hasegawa H, Takenaka K, Utsunomiya T, et al. Postoperative liver failure after major hepatic resection for hepatocellular carcinoma in the modern era with special reference to remnant liver volume. *J Am Coll Surg.* 1999;188:304–9.
5. van den Broek MA, Olde Damink SW, Dejong CH, Lang H, Malagó M, Jalan R, et al. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. *Liver Int.* 2008;28:767–80.
6. Farges O, Belghiti J, Kianmanesh R, Regimbeau JM, Santoro R, Vilgrain V, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. *Ann Surg.* 2003;237:208–17.
7. Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, 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.* 2012;255:405–14.
8. Guiu B, Chevallier P, Denys A, Delhom E, Pierredon-Foulongne MA, Rouanet P, et al. Simultaneous trans-hepatic portal and hepatic vein embolization before major hepatectomy: the liver venous deprivation technique. *Eur Radiol.* 2016;26:4259–67.
9. Abulkhir A, Limongelli P, Healey AJ, Damrah O, Tait P, Jackson J, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. *Ann Surg.* 2008;247:49–57.
10. Madoff DC, Abdalla EK, Vauthey JN. Portal vein embolization in preparation for major hepatic resection: evolution of a new standard of care. *J Vasc Interv Radiol.* 2005;16:779–90.
11. May BJ, Talenfeld AD, Madoff DC. Update on portal vein embolization: evidence-based outcomes, controversies, and novel strategies. *J Vasc Interv Radiol.* 2013;24:241–54.
12. Li D, Madoff DC. Portal vein embolization for induction of selective hepatic hypertrophy prior to major hepatectomy: rationale, techniques, outcomes and future directions. *Cancer Biol Med.* 2016;13:426–42.
13. 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.* 2004;240:1037–49; discussion 1049–51.
14. Thakrar PD, Madoff DC. Preoperative portal vein embolization: an approach to improve the safety of major hepatic resection. *Semin Roentgenol.* 2011;46:142–53.
15. Urata K, Kawasaki S, Matsunami H, Hashikura Y, Ikegami T, Ishizone S, et al. Calculation of child and adult standard liver volume for liver transplantation. *Hepatology.* 1995;21:1317–21.
16. Johnson TN, Tucker GT, Tanner MS, Rostami-Hodjegan A. Changes in liver volume from birth to adulthood: a meta-analysis. *Liver Transpl.* 2005;11:1481–93.
17. Soyer P, Roche A, Elias D, Levesque M. Hepatic metastases from colorectal cancer: influence of hepatic volumetric analysis on surgical decision making. *Radiology.* 1992;184:695–7.
18. van der Vorst JR, van Dam RM, van Stiphout RS, van den Broek MA, Hollander IH, Kessels AG, et al. Virtual liver resection and volumetric analysis of the future liver remnant using open source image processing software. *World J Surg.* 2010;34:2426–33.
19. Lodewick TM, Arnoldussen CW, Lahaye MJ, van Mierlo KM, Neumann UP, Beets-Tan RG, et al. Fast and accurate liver volumetry prior to hepatectomy. *HPB (Oxford).* 2016;18:764–72.
20. Vauthey JN, Abdalla EK, Doherty DA, Gertsch P, Fenstermacher MJ, Loyer EM,

et al. Body surface area and body weight predict total liver volume in Western adults. *Liver Transpl.* 2002;8:233-40.

21. Ribero D, Amisano M, Bertuzzo F, Langella S, Lo Tesoriere R, Ferrero A, et al. Measured versus estimated total liver volume to preoperatively assess the adequacy of the future liver remnant: which method should we use? *Ann Surg.* 2013;258:801-6; discussion 806-7.

22. Leung U, Simpson AL, Araujo RL, Gönen M, McAuliffe C, Miga MI, et al. Remnant growth rate after portal vein embolization is a good early predictor of post-hepatectomy liver failure. *J Am Coll Surg.* 2014;219:620-30.

23. Martel G, Cieslak KP, Huang R, van Lienden KP, Wiggers JK, Belblidia A, et al. Comparison of techniques for volumetric analysis of the future liver remnant: implications for major hepatic resections. *HPB (Oxford).* 2015;17:1051-7.

24. Kokudo T, Hasegawa K, Uldry E, Matsuyama Y, Kaneko J, Akamatsu N, et al. A new formula for calculating standard liver volume for living donor liver transplantation without using body weight. *J Hepatol.* 2015;63:848-54.

25. Shaw BI, Burdine LJ, Braun HJ, Ascher NL, Roberts JP. A formula to calculate standard liver volume using thoracoabdominal circumference. *Transplant Direct.* 2017;3:e225.

26. Kishi Y, Abdalla EK, Chun YS, Zorzi D, Madoff DC, Wallace MJ, et al. Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. *Ann Surg.* 2009;250:540-8.

27. Vauthey JN, Chaoui A, Do KA, Bilimoria MM, Fenstermacher MJ, Charnsangavej C, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery.* 2000;127:512-9.

28. Nagino M, Nimura Y, Kamiya J, Kondo S, Uesaka K, Kin Y, et al. Changes in hepatic lobe volume in biliary tract cancer patients after right portal vein embolization. *Hepatology.* 1995;21:434-9.

29. Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol.* 2006;24:2065-72.

30. Shindoh J, Tzeng CW, Aloia TA, Curley SA, Zimmitti G, Wei SH, et al. Optimal future liver remnant in patients treated with extensive preoperative chemotherapy for colorectal liver metastases. *Ann Surg Oncol.* 2013;20:2493-500.

31. Lau H, Man K, Fan ST, Yu WC, Lo CM, Wong J. Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. *Br J Surg.* 1997;84:1255-9.

32. Morris-Stiff G, Gomez D, Prasad R. Quantitative assessment of hepatic function and its relevance to the liver surgeon. *J Gastrointest Surg.* 2009;13:374-85.

33. De Gasperi A, Mazza E, Prosperi M. Indocyanine green kinetics to assess liver function: ready for a clinical dynamic assessment in major liver surgery? *World J Hepatol.* 2016;8:355-67.

34. Ohwada S, Kawate S, Hamada K, Yamada T, Sunose Y, Tsutsumi H, et al. Perioperative real-time monitoring of indocyanine green clearance by pulse spectrophotometry predicts remnant liver functional reserve in resection of hepatocellular carcinoma. *Br J Surg.* 2006;93:339-46.

35. Mihara K, Sugiura T, Okamura Y, Kanemoto H, Mizuno T, Moriguchi M, et al. A predictive factor of insufficient liver regeneration after preoperative portal vein embolization. *Eur Surg Res.* 2013;51:118-28.

36. Denys A, Bize P, Demartines N, Deschamps F, De Baere T; Cardiovascular and Interventional Radiological Society of Europe. Quality improvement for portal vein embolization. *Cardiovasc Intervent Radiol.* 2010;33:452-6.

37. Makuuchi M, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunvén P, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. *Surgery.* 1990;107:521-7.

38. Denys A, Madoff DC, Doenz F, Schneider F, Gillet M, Vauthey JN, et al. Indications for and limitations of portal vein embolization before major hepatic resection for hepatobiliary malignancy. *Surg Oncol Clin N Am.* 2002;11:955-68.

39. Kinoshita H, Sakai K, Hirohashi K, Igawa S, Yamasaki O, Kubo S. Preoperative portal vein embolization for hepatocellular carcinoma. *World J Surg.* 1986;10:803-8.

40. Nagino M, Nimura Y, Kamiya J, Kondo S, Kanai M. Selective percutaneous transhepatic embolization of the portal vein in preparation for extensive liver resection: the ipsilateral approach. *Radiology.* 1996;200:559-63.

41. Madoff DC, Abdalla EK, Gupta S, Wu TT, Morris JS, Denys A, 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.* 2005;16:215-25.

42. Di Stefano DR, de Baere T, Denys A, Hakime A, Gorin G, Gillet M, et al. Preoperative percutaneous portal vein embolization: evaluation of adverse events in 188 patients. *Radiology.* 2005;234:625-30.

43. 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.* 2007;94:1386-94.

44. Kodama Y, Shimizu T, Endo H, Miyamoto N, Miyasaka K. Complications of percutaneous transhepatic portal vein embolization. *J Vasc Interv Radiol.* 2002;13:1233-7.

45. Sarwar A, Brook OR, Weinstein JL, Khwaja K, Ahmed M. Trans-splenic portal vein embolization: a technique to avoid damage to the future liver remnant. *Cardiovasc Intervent Radiol.* 2016;39:1514-8.

46. Ko HK, Ko GY, Sung KB, Gwon DI, Yoon HK. Portal vein embolization via percutaneous transsplenic access prior to major hepatectomy for patients with insufficient future liver remnant. *J Vasc Interv Radiol.* 2016;27:981-6.

47. 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 iodinized oil: adequate hypertrophy with a reduced risk of nontarget emboli-zation. *Cardiovasc Intervent Radiol.* 2009;32:471-7.

48. Cotroneo AR, Innocenti P, Marano G, Legnini M, Iezzi R. Pre-hepatectomy portal vein embolization: single center experience. *Eur J Surg Oncol.* 2009;35:71-8.

49. Imamura H, Shimada R, Kubota M, Matsuyama Y, Nakayama A, Miyagawa S, et al. Preoperative portal vein embolization: an audit of 84 patients. *Hepatology.* 1999;29:1099-105.

50. Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. *Ann Surg.* 2006;243:364-72.

51. Fischman AM, Ward TJ, Horn JC, Kim E, Patel RS, Nowakowski FS, et al. Portal vein embolization before right hepatectomy or extended right hepatectomy using sodium tetradecyl sulfate foam: technique and initial results. *J Vasc Interv Radiol.* 2014;25:1045-53.

52. de Baere T, Teriitehau C, Deschamps F, Catherine L, Rao P, Hakime A, et al. Predictive factors for hypertrophy of the future remnant liver after selective portal vein embolization. *Ann Surg Oncol.* 2010;17:2081-9.

53. Giraudo G, Greget M, Oussoultzoglou E, Rosso E, Bachellier P, Jaeck D. Preoperative contralateral portal vein embolization before major hepatic resection is a safe and efficient procedure: a large single institution experience. *Surgery.* 2008;143:476-82.

54. Malinowski M, Geisel D, Stary V, Denecke T, Seehofer D, Jara M, et al. Portal vein embolization with plug/coils improves hepatectomy outcome. *J Surg Res.* 2015;194:202-11.

55. de Baere T, Roche A, Elias D, Lasser P, Lagrange C, Bousson V. Preoperative portal vein embolization for extension of hepatectomy indications. *Hepatology.* 1996;24:1386-91.

56. Shimamura T, Nakajima Y, Une Y, Namieno T, Ogasawara K, Yamashita K, et al. Efficacy and safety of preoperative percutaneous transhepatic portal embolization with absolute ethanol. *Surgery.* 1997;121:135-41.

57. Gibo M, Unten S, Yogi A, Nakayama T, Ayukawa Y, Gibo S, et al. Percutaneous ipsilateral portal vein embolization using a modified four-lumen balloon catheter with fibrin glue: initial clinical experience. *Radiat Med.* 2007;25:164-72.

58. Geisel D, Malinowski M, Powerski MJ, Wüstefeld J, Heller V, Denecke T, et al. Improved hypertrophy of future remnant liver after portal vein embolization with plugs, coils and particles. *Cardiovasc Intervent Radiol.* 2014;37:1251-8.

59. van Lienden KP, van den Esschert JW, de Graaf W, Bipat S, Lameris JS, van Gulik TM, et al. Portal vein embolization before liver resection: a systematic review. *Cardiovasc Intervent Radiol.* 2013;36:25-34.

60. Huisman F, Cieslak KP, van Lienden KP, Bennink RJ, van Gulik TM. Liver related complications in unresectable disease after portal vein embolization. *Hepatobiliary Surg Nutr.* 2017;6:379-86.

61. Ko GY, Sung KB, Yoon HK, Kim JH, Weon YC, Song HY. Preoperative portal vein embolization with a new liquid embolic agent. *Radiology.* 2003;227:407-13.

62. Yamashita S, Sakamoto Y, Yamamoto S, Takemura N, Omichi K, Shinkawa H, et al. Efficacy of preoperative portal vein embolization among patients with hepatocellular carcinoma, biliary tract cancer, and colorectal liver metastases: a comparative study based on single-center experience of 319 cases. *Ann Surg Oncol.* 2017;24:1557-68.

63. 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.* 2008;15:2765-72.

64. Deipolyi AR, Zhang YS, Khademhosseini A, Naidu S, Borad M, Sahin B, et al. Portal vein embolization: impact of chemotherapy and genetic mutations. *J Clin Med.* 2017;6:E26.

65. Zeile M, Bakal A, Volkmer JE, Stavrou GA, Dautel P, Hoeltje J, et al. Identification of cofactors influencing hypertrophy of the future liver remnant after portal vein embolization-the effect of collaterals on embolized liver volume. *Br J Radiol.* 2016;89:20160306.

66. Guiu B, Bize P, Gunthern D, Demartines N, Halkic N, Denys A. Portal vein embolization before right hepatectomy: improved results using n-butyl-cyanoacrylate compared to microparticles plus coils. *Cardiovasc Intervent Radiol.* 2013;36:1306-12.

67. Jaberi A, Toor SS, Rajan DK, Mironov O, Kachura JR, Cleary SP, et al. Comparison of clinical outcomes following glue versus polyvinyl alcohol portal vein embolization for hypertrophy of the future liver remnant prior to right hepatectomy. *J Vasc Interv Radiol.* 2016;27:1897-905.e1.

68. Ironside N, Bell R, Bartlett A, McCall J, Powell J, Pandanaboyana S. Systematic review of perioperative and survival outcomes of liver resections with and without preoperative portal vein embolization for colorectal metastases. *HPB (Oxford).* 2017;19:559-66.

69. Olthof PB, Wiggers JK, Groot Koerkamp B, Coelen RJ, Allen PJ, Besselink MG, et al. Postoperative liver failure risk score: identifying patients with resectable perihilar cholangiocarcinoma who can benefit from portal vein embolization. *J Am Coll Surg.* 2017;225:387-94.

70. Simoneau E, Aljiffry M, Salman A, Abualhassan N, Cabrera T, Valenti D, et al. Portal vein embolization stimulates tumour growth in patients with colorectal cancer liver metastases. *HPB (Oxford).* 2012;14:461-8.

71. Kokudo N, Tada K, Seki M, Ohta H, Azekura K, Ueno M, et al. Proliferative activity of intrahepatic colorectal metastases after preoperative hemihepatic portal vein embolization. *Hepatology.* 2001;34:267-72.

72. Giglio MC, Giakoustidis A, Draz A, Jawad ZAR, Pai M, Habib NA, et al. Oncological outcomes of major liver resection following portal vein embolization: a systematic review and meta-analysis. *Ann Surg Oncol.* 2016;23:3709-17.

73. Huiskens J, Olthof PB, van der Stok EP, Bais T, van Lienden KP, Moelker A, et

al. Does portal vein embolization prior to liver resection influence the oncological outcomes: a propensity score matched comparison. *Eur J Surg Oncol.* 2018;44:108–14.

74. Beppu T, Okabe H, Okuda K, Eguchi S, Kitahara K, Taniai N, et al. Portal vein embolization followed by right-side hemihepatectomy for hepatocellular carcinoma patients: a Japanese multi-institutional study. *J Am Coll Surg.* 2016;222:1138–48.e2.

75. Ogata S, Belghiti J, Farges O, Varma D, Sibert A, Vilgrain V. Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma. *Br J Surg.* 2006;93:1091–8.

76. Yoo H, Kim JH, Ko GY, Kim KW, Gwon DI, Lee SG, et al. Sequential transcatheter arterial chemoembolization and portal vein embolization versus portal vein embolization only before major hepatectomy for patients with hepatocellular carcinoma. *Ann Surg Oncol.* 2011;18:1251–7.

77. Peng PD, Hyder O, Bloomston M, Marques H, Corona-Villalobos C, Dixon E, et al. Sequential intra-arterial therapy and portal vein embolization is feasible and safe in patients with advanced hepatic malignancies. *HPB (Oxford).* 2012;14:523–31.

78. Aoki T, Imamura H, Hasegawa K, Matsukura A, Sano K, Sugawara Y, et al. Sequential preoperative arterial and portal venous embolizations in patients with hepatocellular carcinoma. *Arch Surg.* 2004;139:766–74.

79. Esch JS, Schmelzle M, Fürst G, Robson SC, Krieg A, Duhme C, et al. Infusion of CD133+ bone marrow-derived stem cells after selective portal vein embolization enhances functional hepatic reserves after extended right hepatectomy: a retrospective single-center study. *Ann Surg.* 2012;255:79–85.

80. Treska V, Liska V, Fichtl J, Lysak D, Mirka H, Bruha J, et al. Portal vein embolisation with application of haematopoietic stem cells in patients with primarily or non-resectable colorectal liver metastases. *Anticancer Res.* 2014;34:7279–85.

81. Ludvík J, Duras P, Třeška V, Matoušková T, Brůha J, Fichtl J, et al. Portal vein embolization with contralateral application of stem cells facilitates increase of future liver remnant volume in patients with liver metastases. *Cardiovasc Intervent Radiol.* 2017;40:690–6.

82. Fausto N, Campbell JS, Riehle KJ. Liver regeneration. *J Hepatol.* 2012;57:692–4.

83. Kim SJ, Kim DG, Lee MD. Effects of branched-chain amino acid infusions on liver regeneration and plasma amino acid patterns in partially hepatectomized rats. *Hepatogastroenterology.* 2011;58:1280–5.

84. Huang W, Ma K, Zhang J, Qatanani M, Cuvillier J, Liu J, et al. Nuclear receptor-dependent bile acid signaling is required for normal liver regeneration. *Science.* 2006;312:233–6.

85. Beppu T, Nitta H, Hayashi H, Imai K, Okabe H, Nakagawa S, et al. Effect of branched-chain amino acid supplementation on functional liver regeneration in patients undergoing portal vein embolization and sequential hepatectomy: a randomized controlled trial. *J Gastroenterol.* 2015;50:1197–205.

86. Olthof PB, Huisman F, Schaap FG, van Lienden KP, Bennink RJ, van Golen RF, et al. Effect of obeticholic acid on liver regeneration following portal vein embolization in an experimental model. *Br J Surg.* 2017;104:590–9.

87. Mangieri CW, McCartt JC, Strode MA, Lowry JE, Balakrishna PM. Perioperative hepatocyte growth factor (HGF) infusions improve hepatic regeneration following portal branch ligation (PBL) in rodents. *Surg Endosc.* 2017;31:2789–97.

88. Gruttadauria S, Gridelli B. Sequential preoperative ipsilateral portal and arterial embolization in patients with liver tumors: is it really the best approach? *World J Surg.* 2007;31:2427–8.

89. Guiu B, Quenet F, Escal L, Bibeau F, Piron L, Rouanet P, et al. Extended liver venous deprivation before major hepatectomy induces marked and very rapid increase in future liver remnant function. *Eur Radiol.* 2017;27:3343–52.

90. Le Roy B, Perrey A, Fontarensky M, Gagnière J, Abergel A, Pereira B, et al. Combined preoperative portal and hepatic vein embolization (Biembolization) to improve liver regeneration before major liver resection: a preliminary report. *World J Surg.* 2017;41:1848–56.

91. Tranchart H, Koffi GM, Gaillard M, Lainas P, Poüs C, Gonin P, et al. Liver regeneration following repeated reversible portal vein embolization in an experimental model. *Br J Surg.* 2016;103:1209–19.

92. Wirsching A, Melloul E, Lezhnina K, Buzdin AA, Ogunshola OO, Borger P, et al. Temporary portal vein embolization is as efficient as permanent portal vein embolization in mice. *Surgery.* 2017;162:68–81.

93. Olthof PB, Huisman F, van Golen RF, Cieslak KP, van Lienden KP, Plug T, et al. Use of an absorbable embolization material for reversible portal vein embolization in an experimental model. *Br J Surg.* 2016;103:1306–15.

94. Tranchart H, Catherine L, Maître S, Lainas P, De Laveaucoupet J, Dagher I. Efficient liver regeneration following temporary portal vein embolization with absorbable gelatin sponge powder in humans. *J Vasc Interv Radiol.* 2015;26:507–15.