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Portal vein embolization: rationale, techniques, outcomes and novel strategies

The incidence of liver cancer has grown in the past decade, with 905,677 new cases and 830,180 deaths in 2020. According to the highest annual fatality ratio, liver cancer is the third-leading cause of cancer-related deaths worldwide. Surgical resection is the mainstay treatment for long-term survival. However, only 25% of patients are surgical candidates. Recent surgical concepts, techniques and multidisciplinary management were developed, including interventional radiology procedures that improve the management algorithm, expand the indications and limit dropouts from curative treatment. This review summarizes up-to-date information on interventional radiology in the management of liver tumors.

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Surgical resection is a major curative therapy for patients with liver malignancy, both primary liver cancers and metastases. However, fewer than 25% of patients are surgical candidates [2,3]. The most important factor to consider before resection is whether the future liver remnant (FLR) is sufficient to support postoperative liver function. Inadequate volume of the liver after surgery has been shown to be a strong, independent predictor of postoperative hepatic dysfunction and complications [4]. Preoperative portal vein embolization induces hepatocyte regeneration, thereby allowing 78–80% of patients to undergo major hepatectomy [5,6]. Hepatocyte regeneration occurs after injury from vascular occlusion through multiple factors including the release of nitrous oxide stimulated by portal pressure changes, intrahepatic growth factors, tumor necrosis factor α (TNF- α), and gut-derived growth factors carried by the portal vein [7].

Patient selection, hepatic volumetry & methods to assess hepatic function

The adequacy of the FLR should be assessed using both the remnant volume and the remnant liver function. The FLR volume can be assessed with the FLR ratio, which can be calculated as FLR volume/total liver volume (TLV). Another technique described by Vauthey *et al.* [8], calculates estimated FLR as FLR volume/estimated TLV using the patient's body surface area (BSA), where the estimated TLV = $-794.41 + (1267.28 \times \text{BSA})$. Although the latter method does not require the volume of the entire liver, it demonstrates a significant difference in volumetry compared with the FLR ratio technique [9]. Recently, many automated liver volumetry methods have been developed, including artificial intelligence methods [10–12]. Patients with normal liver function and an FLR ratio >20% demonstrate significantly less postoperative complications [13,14]. The FLR ratio is expected to be >30% in patients who either received hepatotoxic chemotherapy or have hepatic steatosis and to be >40% in cirrhotic patients. Preoperative portal vein embolization is indicated in cases where the FLR ratio is insufficient (Figure 1).

The function of the liver remnant can be assessed with the indocyanine green (ICG) clearance test, asialoglycoprotein receptor scintigraphy with ^{99m}Tc-galactosyl human serum albumin and measurement of serum hyaluronic acid level [15,16]. ICG is a tricarbocyanine dye that binds with albumin and distributes it in the blood pool after injection. ICG is eliminated from the body exclusively by biliary excretion. The degree of excretion can be accessed



Figure 1. Axial computed tomography scan of the liver in portovenous phase. Multiple hypodense masses are present in the right hepatic lobe. The future liver remnant indicated in blue color area, which the volume is not sufficient.

by serum blood test or via an optical sensor placed on the finger. Typically, less than 10% of the ICG should remain in the blood 15 min after injection (ICG-R15). The plasma disappearance rate of ICG (ICGK) is another useful parameter, with blood samples collected at 5, 10 and 15 min after ICG injection. The ICGK is calculated using linear regression analysis of the plasma ICG concentration [17]. There are many proposed criteria to predict cutoff levels for safe hepatic resection (e.g., Makuuchi's criteria) [18–21]. Contraindications are severe portal hypertension, uncontrollable intrahepatic portal to hepatic vein shunts, tumor thrombus in the portal vein and occlusion of the portal vein in FLR. Patients with metastatic disease, such as distant metastases or periportal lymphadenopathy, cannot undergo resection, and therefore are not candidates for portal vein embolization.

Technical considerations

Methods for portal access

Portal vein embolization can be performed by surgical transileocolic approach or percutaneous transhepatic approach. The percutaneous transhepatic approach can be accessed ipsilateral or contralateral to the tumor-bearing hepatic lobe. The contralateral approach allows easier catheter manipulation and deployment of embolic materials, but the puncture through the FLR results in direct damage to the parenchyma and vessels. The advantage of the ipsilateral approach is a low risk of FLR damage, but there are risks of complications if the tumor is located in the trajectory of the puncture. Therefore, the contralateral approach is usually performed if there is no safe route for ipsilateral access. For the ipsilateral approach, anterior branches of the right portal vein are the preferred target due to a low complication rate [22]. Percutaneous transsplenic access has also been proposed with an 88.9% chance of technical success and a 3.8% chance of major complications (splenic vein dissection) [23]. Recently, access through the round ligament has also been reported without morbidity or mortality [24].

Embolization techniques

After access to the portal vein, a catheter will be advanced to the splenic vein/SMV confluence. A pigtail catheter is preferred for large volume contrast injection for portography to assess the anatomical pattern and target the embolized branches (Figure 2). The target vessels for embolization before right hepatectomy are the right portal branches supplying the right lobe. In cases of extended right hepatectomy, there has been controversy about additional embolization of segment four due to the difficulty catheterizing into the feeding branches and the risk of inadvertent embolization to the FLR. But many studies have shown improved hypertrophy of segments two and three as well as a higher kinetic growth rate with the additional embolization of segment four compared with embolization of the right portal vein alone [25–27]. Ito *et al.* demonstrated hypertrophy of segments two and three in patients who underwent right portal vein embolization with and without segment four of 52.4% versus 32.2%, respectively, and kinetic growth rates of 3.1% per week versus 2.0% per week [26]. Contrast-enhanced computed tomography (CT) volumetry is performed 4–7 weeks after portal vein embolization to assess the FLR (Figure 3).

Embolic materials

Various embolic materials are available for portal vein embolization, including gelatin sponges, polyvinyl alcohol (PVA) particles, microspheres, N-butyl cyanoacrylate (NBCA), absolute ethanol and sodium tetradecyl sulfate foam with or without combination with coils or vascular plugs (Table 1). There is no consensus regarding a

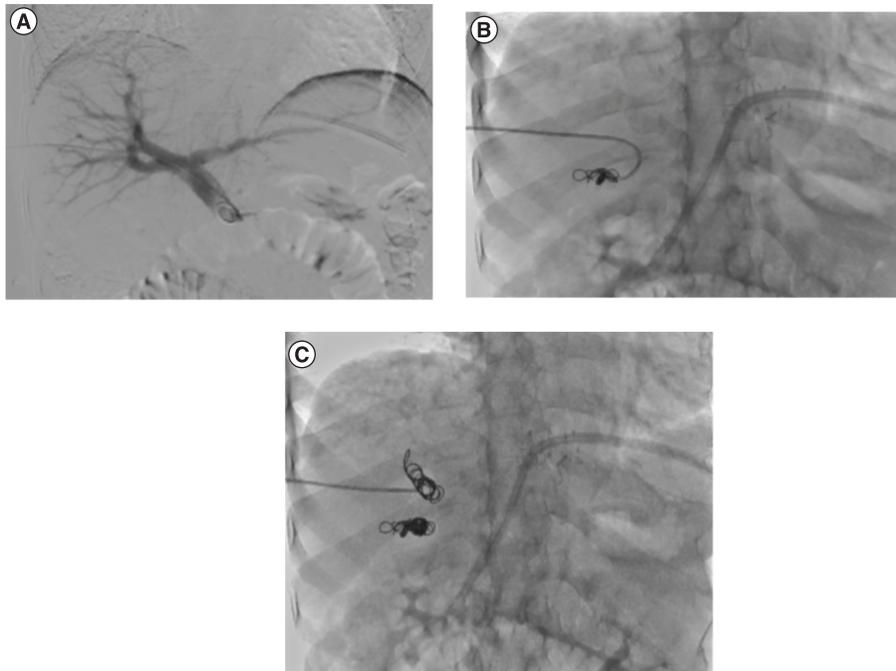


Figure 2. Portal vein embolization techniques. (A) A pigtail catheter is advanced to main portal vein, and portogram was performed. **(B & C)** Selective embolization of the target branches with coils after achieved distal embolization with preferred embolic materials.

Embolic agent	Increase FLR (%)	Increase FLR/TLV (%)	Kinetic growth rate (%/week)	Ref.
Gelatin sponge, slurried	23.7	N/A	N/A	[31]
Gelatin sponge powder	29.4	6.3	7.35	[30]
Gelatin sponge powder + iodized oil	37	10.2	18.5	[29]
Gelatin sponge, slurried + coils	30.7–36.7	9.4	N/A	[31,36]
Absolute ethanol	40	12	N/A	[37]
NBCA	24–29.1	10–12.5	1.4	[38,39]
NBCA + vascular plug	49.6	16.2	3.5	[40]
PVA + coil	40.2–45.5	6.9–12.3	N/A	[33,40,41]
Microsphere + coil	69	9.7	N/A	[41]
STS	25.7–48.8	9.9–11.9	N/A	[38,42]

FLR: Future liver remnant; NBCA: N-butyl cyanoacrylate; PVA: Polyvinyl alcohol; STS: Sodium tetradecyl sulfate.

standard embolization agent to be used for portal vein embolization. The ideal technique achieves complete portal occlusion of the target segments by creating distal embolization to constrain the development of intrahepatic collateral circulation from backflow, and proximal embolization to prevent venous inflow, which likely diminishes hypertrophy of the FLR.

Gelatin sponge

Theoretically, gelatin sponge is not an ideal material due to the temporary embolization property, which may result in recanalization of the embolized portal segments and limiting of FLR hypertrophy. In the early era of portal vein embolization, few studies reported less hypertrophy. De Baere *et al.* [28] reported a 53% increase FLR when using gelatin sponge compared with a 69% increase FLR when used cyanoacrylate. The preparation of the gelatin sponge was done by cutting the material into a 20 × 2 mm block and mixing it with a contrast medium. The product achieved by this preparation should be large and irregular in size, which causes proximal occlusion rather

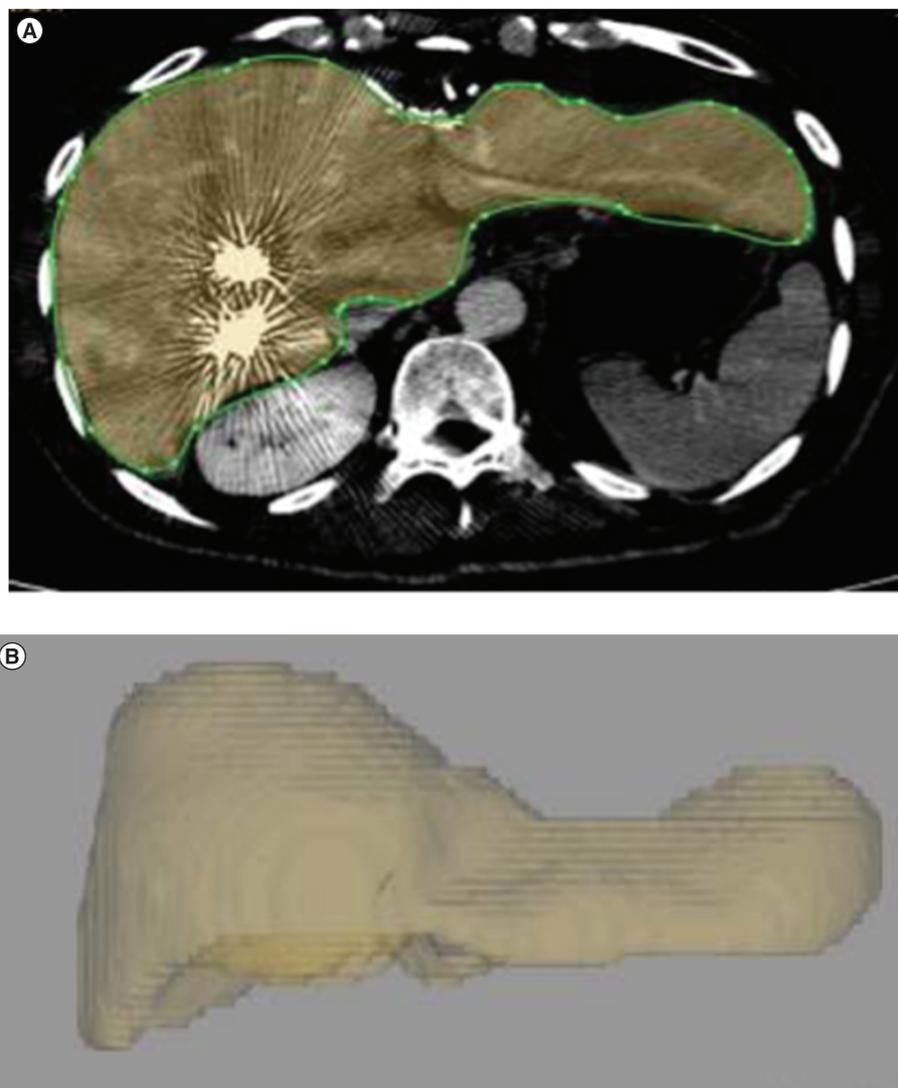


Figure 3. Post-operative computed tomography volumetry. (A) Axial view shows coils in the embolized portal branches. (B) 3D-volume rendering of the same patient to evaluate the future liver remnant volume.

than distally blocking the backflow. In 1999, Imamura *et al.* reported the results of 84 patients who underwent preoperative portal vein embolization using 200–600 μm gelatin sponge powder mixed with 500–2500 units of thrombin, 10–20 ml of diatrizoate sodium meglumine, 1.5–2 ml of suspended ionized oil and 40 mg of gentamicin, which achieved a 37% increase in FLR volume within two weeks after portal vein embolization. They reported one case of complete recanalization of the embolized portal vein with a subsequent low degree of hypertrophy (28%) [29].

Later, the concept of temporary portal vein embolization was introduced. The rationale for this approach is that the kinetics of liver hypertrophy after portal vein occlusion mostly occurs in 2–3 weeks, then reaches the plateau of the curve. The recanalization of the embolized portal vein using a gelatin sponge is expected within 2 weeks, which would not preclude liver hypertrophy. The advantages of temporary embolization are decreased permanent damage to the FLR in cases of nontarget embolization and recanalization of the portal vein to minimize injury to the embolized liver if the patient finally does not undergo liver resection. Tranchart *et al.* reported the efficacy of portal vein embolization using gelatin sponge powder as a 29.4% increase in FLR and a 6.9% increase in FLR/TLV. But there was no comparative embolic material in that study [30]. In 2015, Shin *et al.* reported superior efficacy of portal vein embolization using gelatin sponge (which was cut into 1–2 mm and slurried by vigorous manual pumping between syringes) combined with coils compared with gelatin sponge alone (increase FLR 36.7 vs 23.7%;

$p = 0.02$). Expectedly high recanalization was demonstrated (40% vs 88.2%; $p = 0.003$) [31]. To date, only limited use of gelatin sponge alone has been reported due to the superiority of other permanent embolic materials [32].

Polyvinyl alcohol

Polyvinyl alcohol (PVA) particles are available in various sizes, ranging from 45 to 1000 μm . In commercial packaging, the particles are mixed in a short range of sizes (e.g., 355 to 500 μm). According to their irregular shape, clumping may occur and cause proximal embolization. A combination of PVA (for distal embolization) and coils (for proximal embolization to prevent venous inflow) is widely used. Camelo *et al.* reported an increased FLR volume of 40%, and an increased FLR/TLV ratio of 11%, $p < 0.001$) [33].

Microspheres, another type of permanent particle material, are known to be regular in size, spherical in shape and compressible. These properties promote more distal embolization.

N-butyl cyanoacrylate

N-butyl cyanoacrylate (NBCA) is a liquid embolic agent, supplied in 0.5–1.0 ml vials. Polymerization occurs with contact to ionic mediums, forming a strong bond to adjacent tissues. Catheters must be flushed with nonionic liquids, (e.g., dextrose in water), to avoid NBCA polymerization inside the lumen. Dilution with lipiodol slows the polymerization, allowing the material to flow to distal portions of vessels before polymerizing. Various lipiodol-NBCA ratios are selected based on the portal flow, vascular diameter and level of target embolization. NBCA causes significant peripheral inflammation and produces effective portal occlusion. A recent randomized controlled trial compared the efficacy of portal vein embolization using NBCA versus PVA with coils and demonstrated that NBCA showed greater and faster liver growth (FLR increased 57 vs 37%, and kinetic growth rate 4% per week vs 3% per week, respectively) [34].

Absolute ethanol

Ethanol is a sclerosant to vascular epithelium through protein denaturation with subsequent immediate thrombus formation. The agent shows cytotoxic effects on the surrounding liver parenchyma. Due to the difficulty controlling its flow and reflux, Ethanol is frequently used via the contralateral approach with an occlusion balloon catheter to prevent nontarget damage. A retrospective study showed a significant increase in the ratio of embolized liver volume/total functional liver volume with the use of absolute ethanol compared with NBCA (13% vs 9.5%). These increased ratios are from severe atrophic effects upon the embolized liver, but no significant difference in hypertrophy of the FLR was found, and grade 3 and 4 toxicities were seen more often in the absolute ethanol group [35].

Sodium tetradecyl sulfate

Sodium tetradecyl sulfate (STS) is a liquid sclerosant that is converted into foam when used by mixing with air. This form allows the STS to contact the vascular endothelium more effectively than in liquid form. The agent is an anionic surfactant that affects lipid molecules in the vascular endothelium, resulting in inflammation with subsequent sclerosis.

Inadequate future liver remnant hypertrophy

In general, FLR hypertrophy occurs over the first 3–4 weeks with maximal volume by 6 weeks. However, liver regeneration can be variable, ranging from 28% to 46% at 4 weeks after embolization. In patients with comorbidities, such as underlying hepatic dysfunction or diabetes, FLR hypertrophy by portal vein embolization alone may not be adequate. Furthermore, there is a significant inverse correlation between tumor volume and FLR hypertrophy. This is because colorectal liver metastases increase hepatic arterial blood flow and decrease the liver's dependence on portal perfusion [43]. Combination treatments are available for the promotion of FLR hypertrophy in these cases.

Transarterial embolization

Sequential transarterial chemoembolization and portal embolization have been widely used for the management of hepatocellular carcinoma. The procedure results in occlusion of arterial flow that limits the development of arteriportal shunts that may lower the hypertrophic outcome of the FLR. Tissue necrosis subsequently stimulates liver hypertrophy [44]. Furthermore, after portal vein embolization, there is decreased resistance and increased flow through the hepatic artery in the embolized segment (so-called hepatic artery buffer response). These dynamic

Table 2. Preliminary outcomes of hepatic vein embolization.

Study	Patients	Increase FLR (%)	Increase FLR/TLV (%)	Kinetic growth rate (%/week)	Ref.
Kobayashi <i>et al.</i>	20	89.0	8.0	2.9	[39]
Le Roy <i>et al.</i>	72	51.2	10.0	19.0	[49,50]
Khayat <i>et al.</i>	17	68.7	10.0	N/A	[56]
Panaro <i>et al.</i>	13	N/A	9.6	16.0	[51]

FLR: Future liver remnant; TLV: Total liver volume.

alterations accelerate the growth of hepatocellular carcinoma which often receives blood supply from the hepatic artery. Transarterial chemoembolization, therefore, provides locoregional control before surgery.

Conversely, the transarterial bland embolization (TAE) method is not widely used in hepatic metastases due to the increased risk of liver abscess from liver ischemia. The reported embolization materials used in TAE are ethanol [45] (side effects: postembolization syndrome, prolonged abnormal liver function test and liver abscess; increased FLR 22–46%), microparticles, absorbable gelatin sponge and coils (serious side effect: one fatal sepsis from ascending biliary infection in a patient with a biliary catheter was reported, showing increased FLR: 46.8%) [46,47].

Hepatic vein embolization

Hepatic vein embolization, also known as liver venous deprivation (LVD) is another adjunct. The rationale for this procedure is to create outflow obstruction and induce further damage to the embolized hepatic lobe with avoidance of extensive ischemia. Portal embolization and hepatic vein embolization are performed in the same procedure. The embolization material is a vascular plug that is 80–100% larger than the selected hepatic vein. The increased FLR was 51.2–89% [39,48–50] with no report of posthepatectomy liver failure. There was no difference in terms of morbidity rates in the peri- and postoperative periods between portal vein embolization alone and LVD [51]. Preliminary outcomes are shown in Table 2. Currently, the Dragon trial, investigating the safety and feasibility of the double-vein embolization for patients with colorectal metastases, is enrolling patients.

Portal vein embolization with stem cell application

Hematopoietic stem cells have been used in a variety of diseases and play important roles in tissue maintenance and regeneration, including supporting hepatic progenitor cells in liver regeneration through secretion of cytokines, increased angiogenesis, inhibition of apoptosis and enhancement of tissue proliferation. There are two techniques for stem cell collection. The first is to stimulate the stem cells by granulopoiesis growth factors through subcutaneous administration and monitoring of hematopoietic stem cells in the peripheral blood. Next, large-scale leukapheresis is performed, obtaining a hematopoietic-rich stem cell product. Portal vein embolization is performed one day before the leukapheresis. The rich hematopoietic stem cell product is then administered via the ileocolic vein into the FLR portal vein. The second technique uses bone marrow. The aspirated bone marrow is centrifuged and hematopoietic stem cells are separated out. The product is then administered through the FLR portal vein. Ludvik *et al.* reported higher FLR volumes after portal vein embolization with hematopoietic stem cell administration compared with portal vein embolization alone (173.2 vs 98.9 ml; $p = 0.015$) and higher mean daily growth (7.6 vs 4.1 ml; $p = 0.007$). There was no significant difference in the growth of metastases between groups in the study [52].

Surgical & oncological outcomes

Although the rationale for portal vein embolization and the technical outcomes in terms of increased FLR seems promising, only 66% of patients eventually underwent planned liver resection [53]. The major cause of unresectability is disease progression. As portal vein embolization is achieved, the portal flow reduction stimulates arterial blood flow and decreased hepatic arterial resistance as compensation. These hemodynamic alterations result in increased blood supply to metastases. This progression would not be clinically relevant if the tumor progressed only in the embolized lobe, but these processes affect the entire liver and may also stimulate micrometastases in the FLR and increase the risk of recurrence. However, many recent systematic reviews demonstrated no difference in postoperative hepatic recurrence or overall survival at 3 and 5 years in patients who underwent PVE before surgery compared with those who underwent surgery without PVE [54,55].

Several studies have analyzed the effect of PVE on disease-free survival with controversial results, showing both unaffected and compromised disease-free survival. The PVE group shows less nonliver-specific median disease-free

survival in the series (15.2 vs 21.7 months). The number of patients receiving adjuvant chemotherapy in the PVE group was less than the non-PVE group (40 vs 70%). The reasons for not receiving chemotherapy were multifactorial and included patient nonconsent, no margin involvement at the time of resection and previous neoadjuvant chemotherapy [55]. Ardito *et al.* reported that the liver-specific disease-free survival showed patients in the PVE group had experienced a recurrence of colorectal liver metastases much earlier than those without PVE [56].

To overcome postoperative hepatic recurrence, liver transplantation is still the best option for eligible patients, particularly in patients with a high tumor load. The procedure achieves 5-year overall survival of 45.3% compared with 12.5% in patients who underwent PVE before surgery [57]. Despite undergoing portal vein embolization, about 10% of patients developed postoperative liver failure, which is similar to the non-PVE group (9%), while there was a significantly higher mean total tumor volume in the PVE group [55].

A recent observational retrospective study reporting oncologic outcomes after LVD in patients with colorectal metastases showed that overall survival at 1 and 3 years were 87% and 60.3%, respectively, with a median disease-free survival of 6 months [58]. Surgical outcomes of LVD have been reported. Panaro *et al.* demonstrated no difference in terms of intraoperative bleeding, hepatic pedicle clamping, intraoperative red blood cell transfusion or operative time between patients who underwent only portal vein embolization before surgery versus those who underwent LVD [51].

Complications

Postembolization syndrome, comprised of malaise and low-grade fever, is common in portal vein embolization. The overall complication rate is about 2–9%, which is similar to other transhepatic procedures and includes portal vein thrombosis, hemoperitoneum, subcapsular hematoma, pseudoaneurysm, hemobilia, pneumothorax and cholangitis. Specific complications related to portal vein embolization are inadvertent embolization and recanalization. Typically, the portal pressure increases by 3–5 mmHg after portal vein embolization [59]. Portal hypertension can occur, but usually without clinical significance if the rise in portal venous pressure is moderate (5–7 mmHg) [60]. Nonetheless, in cirrhotics or patients with portal hypertension, these hemodynamic alterations can increase the risk of rupture of gastroesophageal varices. Bilbao *et al.* reported a patient with cirrhosis who suffered from ruptured esophageal varices after portal vein embolization. Transjugular intrahepatic portosystemic shunt was performed immediately [61].

Other available options to increase surgical eligibility

Portal vein ligation

Right portal vein ligation to enhance FLR hypertrophy, either intraoperatively as the initial stage of two-stage hepatectomy, or as an isolated procedure by the exploratory or laparoscopic approach [62], has been performed. Many studies showed no difference in FLR hypertrophy and morbidity between portal vein ligation and portal vein embolization [63,64]. However, one study found less FLR hypertrophy after portal vein ligation compared with portal vein embolization (123 vs 188 ml; $p = 0.012$) with a significantly shorter hospital stay for portal vein embolization (4 vs 8.1 days; $p < 0.01$) [65]. The patients in the study planned for extended right hepatectomy, therefore embolization of the segment four portal branches was achieved. Portal branches responsible for segment four have great variation, with only 2.9% arising from the right portal vein [66]. Thus, ligation of the right portal vein would not efficiently cut the portal supply to segment four. This could explain the inferiority in FLR hypertrophy of the portal vein ligation group. Another explanation is that ligation of the right portal vein only shuts the portal inflow. The distal vascular portions are patent to recruit intrahepatic collaterals, which leads to recanalization of the vessels.

Two-stage hepatectomy

This procedure is performed in patients with bilobar hepatic masses, particularly colorectal liver metastases. The rationale for this procedure is that the liver grows in the interval between the surgery sessions, preventing postoperative liver failure from inadequate FLR. Ineligibility to proceed to the second stage is reported about 8–31% according to tumor progression and inadequate FLR hypertrophy. Postoperative morbidity and mortality after the second stage were 40 and 3%, respectively. Median survival was 16 months. The 3-year disease-free survival rate was 6–27% [67].

Associated liver partition & portal vein ligation for staged hepatectomy

Associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) is another two-stage hepatectomy, in which the first stage is for induction of FLR hypertrophy, and the second stage is to remove the mass. Additional procedures in addition to the traditional two-stage hepatectomy, including ipsilateral portal vein ligation and *in situ* splitting of liver parenchyma, are performed in the first stage to enhance the FLR hypertrophy. A systematic review demonstrated greater FLR hypertrophy in ALPPS compared with traditionally staged hepatectomy (RR = 4.87; 95% CI: 3.41–6.33), more frequent completion of stage 2 resection (RR = 1.32; 95% CI: 1.21–1.44) and a higher mortality rate (10 vs 5%; RR = 2.26; 95% CI: 0.88–5.80) [68,69].

Conclusion

Portal vein embolization is an important multidisciplinary tool that increases surgical eligibility, allows for more extensive surgery and decreases postoperative liver failure for patients with liver tumors. Novel techniques and adjuncts have been developed and are continuing to improve outcomes.

Future perspective

Better understanding of tumor biology and contributing stimulatory environmental factors promoting tumor growth in order to predict patients at risk of tumor progression after portal vein embolization remains to be determined. The role and timing of therapeutic procedures including chemotherapy need to be evaluated with larger-scale studies.

Executive summary

- The adequacy of the future liver remnant (FLR) should be assessed with both remnant volume and remnant liver function. These are comprised of FLR volume, biochemical parameters and functional reserve.
- The contralateral approach is usually performed if there is no safe route for ipsilateral access.
- Additional embolization of segment 4 portal branches should be done in cases of extended right hepatectomy in order to improve hypertrophy of the FLR.
- Ideal portal embolization is to perform distal embolization to constrain the development of intrahepatic collaterals from backflow and proximal embolization to prevent venous inflow.
- The major cause of unresectability after polyvinyl alcohol (PVE) is disease progression. A multidisciplinary team approach is vital in treatment planning, including neoadjuvant chemotherapy.
- Patients with larger tumor burdens who underwent PVE experienced no difference in overall survival at three and five years compared with those who underwent surgery without PVE.

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