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• *REVIEW* •

Portal vein embolization before major hepatectomy

Hai Liu, Yong Fu

Hai Liu, Yong Fu, Department of Surgical Oncology, Hainan Provincial People's Hospital, Haikou 570311, Hainan Province, China
Correspondence to: Dr. Hai Liu, MD, Department of Surgical Oncology, Hainan Provincial People's Hospital, Haikou 570311, Hainan Province, China. dr_liuhai@hotmail.com
Telephone: +86-898-68642223 Fax: +86-898-68653685
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Abstract

To discuss the rationale, techniques and the unsolved issues regarding preoperative portal vein embolization (PVE) before major hepatectomy. After a systematic search of Pubmed, we reviewed and retrieved literature related to PVE. Preoperative PVE is an approach that is gaining increasing acceptance in the preoperative treatment of selected patients prior to major hepatic resection. Induction of selective hypertrophy of the nondiseased portion of the liver with PVE in patients with either primary or secondary hepatobiliary, malignancy with small estimated future liver remnants (FLR) may result in fewer complications and shorter hospital stays following resection. Additionally, PVE performed in patients initially considered unsuitable for resection due to lack of sufficient remaining normal parenchyma may add to the pool of candidates for surgical treatment. The results suggest that PVE is recomm-endable in treating the cirrhotic patients before major liver resection.

Key words: Portal vein embolization; Hepatectomy

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INTRODUCTION

Complete resection of hepatic tumors remains the first choice for curative treatment of primary and secondary liver malignancies, giving the patient the only chance of long-term survival. In up to 45% of primary and secondary liver tumors, extended liver resection is necessary to achieve clear resection margins[1]. The reason for unresectability is that often the remnant liver is of insufficient volume to support postoperative liver function, which itself is still the principal cause of postoperative death after major hepatectomy. The mortality rate after major liver resection ranges from 3.2% to 7% in patients with noninjured liver parenchyma and increases up to 32% in patients with cirrhosis[1-3]. It has been demonstrated that liver failure is directly related to the size of remnant functional liver volume, and various procedures have been developed to induce liver regeneration. Preoperative occlusion of the portal vein branches feeding the hepatic segments to be resected reduced the risk of postoperative liver failure after major liver resection and increased the number of resectable patients[2-4].

Pathophysiological characteristics of liver after PVE

Portal vein ligation (PVL) not only led to atrophy of the ipsilateral lobe and hypertrophy of contralateral lobe in rats[5], but also led to ipsilateral lobe atrophy and contralateral lobe hypertrophy in humans[1,6,7]. These basic observations provide the foundation for the study of portal vein embolization (PVE) for clinical purpose. The mechanisms underlying the atrophy-hypertrophy complex are poorly understood. The liver cells have the remarkable ability to dedifferentiate and expand clonally. Stimuli leading to hypertrophy include a combination of hepatic and extrahepatic factors. The physiological trigger for hypertrophy is unknown. Some cytokine, such as hepatocyte growth factor (HGF), transforming growth factor, and interleukin-6 may be involved[8]. Insulin and glucagon are both two natural nutrient factors for liver cells and the increase of insulin and glucagon may contribute to the hypertrophy of future liver remnant (FLR) after PVE. Immediately after embolization, portal vein blood flow to the unembolized liver measured by transcutaneous Doppler ultrasonography increased significantly, and the resulting hypertrophy rate correlated with blood flow rate[9-11]. Regeneration rate of non-cirrhotic liver was 12-21 cm^3 per d 2 wk after embolization, about 11 cm^3 per d at 4 wk and 6 cm^3 per d at 32 d. For comparison, the rate was slower at 2 wk in cirrhotic liver, only 9 cm^3 per d[2,12,13]. So, liver resection is always performed 4 wk following PVE. Several reasons could explain the failure of hypertrophy after technically successful PVE, among them are the activity of the underlying chronic liver disease, the presence of diabetes[14], the possible vascular recannulization of the embolized portal vein branches and the presence of major portal hypertension with portosystemic shunts[15,16].

Indications and contraindications for PVE

Indications At present, four factors are important to decide whether and when to perform PVE. First, the ratio of FLR to total estimated liver volume (TELV) should be calculated. Second, cases need to be categorized into those with and those without underlying liver diseases because these factors will determine how much FLR is needed to reduce postoperative morbidity and mortality. The minimum absolute liver volume necessary to support post-resection

hepatic function has not been clearly defined. However, an FLR/TELV ratio of at least 25% is recommended in patients with normal livers, with a ratio of at least 40% in patients in whom the liver is considered stable (e.g., from chronic liver disease or high-dose chemotherapy)[17]. When FLR/TELV ratios are below these levels, PVE may be performed in an attempt to increase FLR volume. Third, the presence of systemic disease such as diabetes mellitus may limit hepatic hypertrophy[14]. Insulin is a comitogenic factor with HGF that often leads to fast rates of regeneration. Fourth, planning for the type and extent of the anticipated surgical procedure (e.g., right hepatectomy and pancreaticoduodenectomy) is important because more functional hepatic reserve may be required to reduce postoperative morbidity. Recent clinical studies show that PVE with two-stage hepatectomy is practicable for patients with multiple metastases in both right and left liver[4]. From above, it comes that the PVE should be considered in the following circumstances: (1) major hepatectomy for patients with chronic liver diseases; (2) extended hemihepatectomy for patients with normal liver; (3) two-stage strategy for patients with multiple bilobar metastases. The FLR ratio is calculated with data obtained by three-dimensional volum-etric computed tomography after PVE with the following formula: FLR/TELV = FLR/(total liver volume-tumor volume)×100%.

Contraindications

Patients with metastatic diseases such as distant metastases or periportal lymphadenopathy cannot undergo resection and therefore are not candidates for PVE. Patients with bilobar multiple metastases were not considered as the candidates for PVE before[18], but recent studies confirm that some of these patients can benefit from PVE in combination with two-stage hepatectomy[4]. Other relative contraindications for PVE include an uncorrectable coagulopathy, tumor invasion of the portal vein, tumor precluding safe transhepatic access, biliary dilatation (in cases of biliary tree obstruction, drainage is recommended), portal hypertension, and renal failure that requires dialysis. PVE in cases of tumor invasion of the portal vein may not be warranted because there may be no significant benefit from the procedure.

Issues regarding clinical practice

Preparation for PVE Prior to PVE, a complete patient history is taken and a thorough physical examination performed. Laboratory studies including complete blood cell count, prothrombin time, liver function tests, and blood urea nitrogen/creatinine levels are essential prior to PVE. If patient has an elevated total bilirubin (>3.0 mg/dL), percutaneous or endoscopic biliary drainage is beneficial. CT scanning is a fundamental radiological investigation prior to PVE, for it documents the extent of disease (i.e., extrahepatic disease or involvement of the planned FLR), FLR size, and portal venous anatomy.

PVE techniques

Percutaneous transhepatic preoperative PVE is the most used routine for PVE nowadays[2-4]. On the day of the procedure, prophylactic broad-spectrum antibiotics (e.g., cefazolin, ceftriaxone sodium) are administered intrave-nously for prevention of biliary sepsis. Although general anesthetic may be requested, the procedure is most often performed with local anesthetic (1% lidocaine hydrochloride) and intravenously administered sedatives that allow the patient to remain conscious. Ultrasonography of the liver is performed to determine the best access route into the portal venous system. Under sterile conditions, access into the portal venous system is gained under ultrasonic or fluoro-scopic guidance or both. The ipsilateral approach (access through the portion of the liver to be resected) is recom-mended so as not to injure the FLR. A portal venous access through tumor should be avoided, for it may exacerbate tumor spread or cause subcapsular hematoma. If the tumor burden is high, the contralateral approach (i.e., access through the FLR) may be used. However, this option must be wei-ghed against the possibility of causing injury to the FLR or the portal veins that supply it. In addition, transileocolical venous approach is an alternative performed by a surgeon at open laparotomy with direct cannulation of ileocolic vein[1]. It is particularly practicable for the patients of colorectal cancer with liver metastasis, for the PVE can be done at the surgery of primary tumor.

Choice of embolic agents

Various substances used have yielded different rates or degrees of hypertrophy of unembolized segments. Gelfoam, coil, cyanoacrylate, polyvinyl alcohol, polydocanal, absolute alcohol, fibrin, and lipiodol are used[3,19-22]. Both gelfoam and coil are always used along with other substances for the embolization of large branches of portal vein[19,20]. Gelatin sponge is a generally used embolic material, but frequent recanalization is found, especially 2 wk after embolization if used alone. Fibrin glue has also been used as an embolic agent, but PVE with fibrin glue is incomplete and it allows recanalization in short time if used alone, whereas fibrin mixed with lipiodol can achieve very good embolic effect[23]. But it is very expensive compared to other embolic agents. Cyanoacrylate has a strong embolic effect and has been used for obliteration of gastric coronary vein and esophageal varices. It ensures PVE, which lasts for 4 wk, but massive peribiliary fibrosis and casting of portal vein may increase operative difficulty technically[21]. Polyvinyl alcohol is safe, it causes little periportal reaction, and generates durable portal vein occlusion while used in combination with coils[19]. PVE with absolute alcohol may be particularly useful for hepatocellular carcinoma, although obvious alteration was found in measured liver function following the embolization. Lipiodol is a common embolic agent used for hepatic artery embolization, and it results in very effective embolization when used in combination with cyanoacrylate[3,20]. Polidocanol induces thrombosis and necrotizing inflammation, so it is used in sclerotherapy for esophageal varices. Comparison of embolic effect between different agents shows that the combination of polidocanol with gelatin sponge achieves the best effects, followed by cyanocrylate, gelatin sponge, and fibrin[20]. The effectiveness and safety of a new embolic agent, Embol-78, have been reported, the mean volume of the FLR increased to 38% in the hepatocellular carcinoma group, and by 46% in the nonhepatocellular carcinoma group[22]. Compared with other embolic agents, the authors think that Embol-78 has several advantages. The partially hydrolyzed

polymer Embol-78 was soluble in a less concentrated ethanol solution and miscible in larger quantities of water-soluble contrast media. The improved radiopacity (190 mg of iodine/mL) was thus adequate to permit monitoring of the embolization process with conventional fluoroscopy instead of digital subtraction angiography. Concern about the systemic toxicity of ethanol was also reduced because of the hydrolysis reaction[22].

Efficiency of PVE

Surgical resection has been recognized as the most effective treatment for patients with colorectal liver metastases. Indeed, the mortality rate after hepatectomy has been reduced to less than 5%, and satisfactory 5-year survival rates after hepatectomy have also been reported up to 30%[21]. However, hepatectomy can be applied only for approximately 10-20% of patients with colorectal liver metastases. Among the factors that are contraindications for hepatectomy, insufficient functional volume of remnant liver after hepatic resection can cause postoperative hepatic failure and it is still an obstacle to a major hepatic resection. As one of the solutions to this dilemma and in order to increase the indications for a major hepatectomy, preoperative PVE has been proposed to induce compensatory hypertrophy of the contralateral FLR in patients with metastatic diseases. Two to eight weeks after PVE, FLR may increase by 20-46% with various embolic agents for patients with or without liver parenchyma disease, and 70-100% patients can undergo hemihepatectomy or extended hemihepatectomy after PVE[3,4,20,22]. PVE not only increases the pool of candidates for hepatectomy, but also decreases significantly the incidence of postoperative complications as well as the intensive care unit stay and total hospital stay after right hepatectomy[2,3]. Therefore, Farges adopted routine performance of PVE before major hepatectomy in patients with chronic liver disease[3]. It was only the patients with tumors confined to hemiliver that were considered as candidates for PVE before. However, the recent clinical studies show that PVE with two-stage hepatectomy is practicable for patients with multiple bilobar metastases[4]. In two-stage strategy, the tumors in the FLR are removed at first operation, then followed by PVE and second hemihepatectomy or extended hemihepatectomy. But this strategy should be limited to patients with no more than three nodules in FLR, which are less than 2.5 cm in diameter each. With two-stage strategy, 70% patients can undergo second hemihepatectomy or extended hemihepatectomy after PVE, and the 3-year survival rate was 53%, which was comparable to that of one-stage group or non-PVE group[4]. Broering *et al*[1], found that PVE and PVL were both feasible and safe methods of increasing the remnant functional liver volume and achieving resectability of extended liver tumors without increasing mortality and morbidity. Ligation or PVE with direct cannulation of ileocolic vein of the tumor bearing portal vein branch is reasonable for the patients with liver metastasis from colorectal cancer, and it can be done at the same surgery of the resection of primary tumor. However, Jaeck *et al*[4], argued against this attitude, holding that (1) development of portal cavernoma with collateral circulation to the ligated lobe reduces the efficiency of portal branch ligation; and (2) development of severe adhesions owing to the hilar diss-ection needed for the ligation of the right portal branch consequently makes it more difficult to perform second hepatectomy.

Complications of PVE

PVE is considerably less toxic than arterial embolization, so side effects are minimal. Signs and symptoms of post-embolization syndrome, such as nausea and vomiting, are rare. Fever and pain are infrequent. Changes in liver function following PVE are usually minor and transient (50% of patients have no appreciable change). When transaminase levels rise, they usually peak at a level less than three times baseline 1-3 d after embolization and return to baseline in 7-10 d, regardless of the embolic materials used. Slight changes in total bilirubin value and white blood cell count may be seen. Synthetic function (e.g., prothrombin time) was almost never affected. But mesenterioportal venous thrombosis occurred in one patient[4]. This patient developed acute gastrointestinal bleeding and encephalopathy, which were conservatively treated, and a later ischemic duodenojejunal stenosis with subsequent mechanical occlusion occurred. It is essential to avoid the reflux of embolizing material into the portal venous branches of the remnant liver. The balloon catheter is designed for this purpose[3,20].

Important unsolved issues regarding PVE

The purpose of PVE is to increase the hepatic functional reserve of FLR as well as its volume[24]. However, there are three major problems facing PVE: (1) PVE stimulates the growth of hepatic tumor[2,25,26]; (2) PVE may fail to increase the volume of FLR in some patients, especially those with fibrotic or cirrhotic liver[3]; (3) Is PVE safe in patients with high-grade varices? The mechanisms of fast tumor growth after PVE are still poorly understood. Kokudo *et al*[26], assessed the proliferative activity of intrahepatic metastases in the embolized liver after PVE in 18 patients with colorectal metastases and found a significantly increased tumor Ki-67 labeling index in the metastases group with PVE compared to hepatic metastases without PVE. It was postulated that the tumor growth after PVE might be controlled by three factors: Malignant potential of the tumors; changes in cytokines or growth factors induced by PVE; and changes in blood supply after PVE. Animal models of portal vein branch ligation demonstrated that HGF-mRNA markedly increased in the non-ligated growing lobe, but was only slightly elevated in the ligated shrinking lobe. Increased tissue levels of HGF might increase the level in plasma, thus stimulating the growth of hepatic tumors. Barbaro *et al*[25], recently noted a significant increase in hepatic tumor volume from colorectal carcinoma after PVE, while hepatic tumor volume from carcinoid tumor was unchanged. Another factor potentially stimulating tumor growth after PVE is increased hepatic arterial blood flow in embolized liver after PVE, for supply of intrahepatic metastases depends solely on arterial blood supply[23]. But these cannot explain why PVE increased hepatic tumor volume from colorectal carcinoma, while did not stimulate the growth of carcinoid tumor. Butyrate is known to stimulate proliferation of normal crypt cells, whereas it induces apoptosis and has antiangiogenic effects on colon cancer cells[27]. Therefore,

the lack of butyrate from portal vein blood may contribute to the increase in hepatic metastasis volume of colorectal carcinoma and, meanwhile, the enrichment of butyrate in FLR may help prevent tumor recurrence in patients treated with two-stage strategy. Hepatic arterial blood flow in embolized liver is increased after PVE and the supply of intrahepatic metastases depends solely on arterial blood supply, so PVE combined with transcatheter arterial embolization (TAE) may help prevent tumor growth and at the same time accelerate the hypertrophy of FLR. Pioneering reports from Inaba *et al*, and Sugawara *et al*, have confirmed that PVE in combination with TAE is safe, effective, and hence recommendable. Portal vein pressure rises about 4 cm H_2O after PVE[22], however, there is no report of PVE-related acute variceal hemorrhage. Liver transplantation is an excellent alternative to liver resection in treating the cirrhotic patient with small oligonodular HCC, but for large HCCs, partial liver resection remains the best therapeutic option for cure because neither liver transplantation nor percutaneous treatments are indicated. So PVE has become an important tool to induce hypertrophy of the FLR before major liver resection in cirrhotic patients.

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