Review Article

Portal Vein Embolization in Preparation for Major Hepatic Resection: Evolution of a New Standard of Care

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Portal vein (PV) embolization (PVE) is gaining acceptance in the preoperative management of patients selected for major hepatic resection. PVE redirects portal blood flow to the intended liver remnant to induce hypertrophy of the nondiseased portion of the liver and thereby reduce complications and shorten hospital stays after resection. This article reviews the rationale and existing literature on PVE, including the mechanisms of liver regeneration, the pathophysiology of PVE, the imaging techniques used to measure liver volumes and estimate functional hepatic reserve, and the technical aspects of PVE, including approaches and embolic agents used. In addition, the indications and contraindications for performing PVE in patients with and without chronic liver disease and the multidisciplinary approach required for the treatment of these complex cases are emphasized.

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Abbreviations: BSA = body surface area, FLR = future liver remnant, HCC = hepatocellular carcinoma, NBCA = n-butyl-2-cyanoacrylate, PV = portal vein, PVE = portal vein embolization, TELV = total estimated liver volume

RECENT advances in hepatobiliary surgical techniques have led to improved outcomes after hepatic resection for liver tumors. However, in many patients, complications such as cholestasis, impaired synthetic function, and fluid retention contribute to prolonged recovery times and extended hospital stays after extensive hepatic resection (1,2). Although the risk of perioperative liver failure is multifactorial, one of the factors associated with this complication is the volume of the liver remnant. Patients who have liver disease in addition to liver tumors and undergo resection of more than 60% of the liver's functional mass and patients with an otherwise normal liver who have more than 75%–80% of the functional liver mass resected are considered at higher risk for postoperative liver complications (2–5).

One strategy advocated to improve the safety of extensive liver surgery in patients with small anticipated liver remnants is preoperative portal vein (PV) embolization (PVE) (5–14). In fact, in most comprehensive hepatobiliary centers, preoperative PVE is now considered the standard of care before major hepatectomy for this subset of patients. PVE redirects portal flow to the intended future liver remnant (FLR) to initiate hypertrophy of the nonembolized segments, and the strategy has been shown to improve the functional reserve of the FLR before surgery. In appropriately selected patients, PVE can reduce postoperative morbidity and enable safe, potentially curative hepatectomy for patients not previously considered candidates for resection based on anticipated marginal FLRs (5–14).

The clinical use of PVE is based on experimental observations first reported in 1920 by Rous and Larimore (15). These investigators studied the consequences of segmental PV ligation in a rabbit model and found progressive atrophy of hepatic segments with occluded PVs and hypertrophy of hepatic segments with patent PVs. Later, clinical studies reported that PV or bile duct occlusion secondary to tumor invasion or ligation leads to atrophy of the ipsilateral liver (ie, the liver to be resected) and hypertrophy of the contralateral liver (ie, the liver to remain in situ after resection) (16–18). In 1986, Kinoshita et al (19) first reported on the use of PVE to limit extension of portal tumor thrombi from hepatocellular carcinoma (HCC) for which transarterial embolization was ineffective. In 1990, Makuuchi et al (10) reported the first use of preoperative PVE performed solely to induce left liver hypertrophy before major hepatic resection in patients with hilar cholangiocarcinoma.

Since these early publications, many investigators have described the use of PVE before resection for HCC, cholangiocarcinoma, and liver metastases. The mechanisms of liver regeneration, indications for PVE, methods of measuring the FLR before and after PVE, technical aspects of PVE (eg, embolic agents, approaches, and compli-

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cations), and potential surgical strategies have been described but are in continual evolution. The purpose of this article is to review the indications for and techniques of PVE before hepatic resection for liver tumors, with an emphasis on strategies to improve outcomes.

MECHANISMS AND RATES OF LIVER REGENERATION

The ability of the liver to regenerate after injury or resection is the basis for preparation for major hepatectomy in a patient with an anticipated small liver remnant. Despite its considerable metabolic load, the liver is essentially a quiescent organ in terms of hepatocyte replication, with only 0.0012%–0.01% of hepatocytes undergoing mitosis at any time (20–22). However, this low cell turnover in the healthy liver can be altered by toxic injury or surgical resection, which stimulates sudden, massive hepatocyte proliferation resulting in recovery of the functional liver mass within 2 weeks after the loss of as much as two thirds of the liver. The regenerative response is typically mediated by the proliferation of surviving hepatocytes within the acinar architecture of the remnant liver.

The molecular and cellular events during liver regeneration result from growth-factor stimulation in response to injury. In the regenerating liver, hepatocyte growth factor, transforming growth factor–α, and epidermal growth factor are important stimuli for hepatocyte replication. Hepatocyte growth factor is the most potent mitogen for hepatocyte replication, and in combination with the other mitogenic growth factors (ie, transforming growth factor–α and epidermal growth factor), can induce the production of cytokines, including tumor necrosis factor–α and interleukin-6, and activate immediate response genes that ready the hepatocytes for cell-cycle progression and regeneration. Insulin is synergistic (ie, comitogenic) with hepatocyte growth factor, which explains the slower regeneration rates seen in patients with diabetes compared with those without diabetes (23,24). Importantly, extrahepatic factors are transported primarily from the gut via the PV and not by the hepatic artery (9,25–27).

The degree of hepatocyte proliferation is directly proportional to the degree of stimulus—ie, a minor liver stimulus will result in only a localized mitotic reaction, but any injury greater than 10% will result in proliferation of cells throughout the liver (28). When more than 50% of the liver is resected, a second, less distinct wave of hepatocyte mitoses is observed. Compared with replication after resection, the peak replication after PVE is delayed approximately 3–4 days, suggesting that the hypertrophy stimulus generated by hepatocyte removal is stronger than the stimulus produced by apoptosis seen after PVE (29).

Also important to the understanding of liver regeneration is the observation that the diseased (ie, cirrhotic) liver has a lower capacity to regenerate than the healthy liver has (29). This may be the result of the diminished capacity of hepatocytes to respond to hepatotropic factors or because parenchymal damage such as fibrosis leads to slower portal blood flow rates (30). Noncirrhotic livers in humans regenerate fastest, at rates of 12–21 cm^3/d at 2 weeks, 11 cm^3/d at 4 weeks, and 6 cm^3/d at 32 days after PVE (24,31). The rates of regeneration are slower (9 cm^3/d at 2 weeks) in patients with cirrhosis, with comparable rates found in patients with diabetes (24,32).

CLINICAL RATIONALE FOR PVE BEFORE MAJOR LIVER RESECTION

Makuuchi and colleagues (10) published the initial experience with preoperative PVE to induce left liver hypertrophy preceding right hepatectomy. Their rationale for the use of PVE in this setting was to (i) minimize the abrupt increase in portal pressure at resection that can lead to hepatocellular damage to the FLR, (ii) dissociate portal pressure–induced hepatocellular damage from direct trauma to the FLR during physical manipulation of the liver at the time of surgery (together, these forms of damage might result in hepatic congestion and postresection dysfunction), and (iii) improve overall tolerance to major resection by increasing hepatic mass before resection to reduce the risk of postresection metabolic changes.

After PVE, changes in liver function test results are typically minor and transient, and half of patients experience no change in liver function test results. When aminotransferase levels do increase, they generally peak at levels less than three times baseline levels 1–3 days after PVE and return to baseline levels within 7–10 days regardless of the embolic agent used (10,11,24,32–35). Slight changes in white blood cell count and total serum bilirubin level may be seen. Synthetic functions (eg, prothrombin time) are almost never affected by PVE.

Portal blood flow to the nonembolized hepatic segments measured by Doppler ultrasound (US) increases significantly and then decreases toward—but does not reach—the baseline value after 11 days. The resultant hypertrophy rate correlates with the portal flow rate (9,30).

PVE is much less toxic than arterial embolization, and side effects are typically minor or absent (9). Fever and pain are infrequent, and nausea and vomiting are even more unusual. This is because PVE produces no distortion of the hepatic anatomy, minimal inflammation except immediately around the embolized vein, and little if any parenchymal or tumor necrosis (10,36). Animal studies reveal that hepatocytes undergo apoptosis (ie, programmed cell death) and not necrosis after portal venous occlusion (37,38), which explains the absence of significant systemic symptoms after PVE.

MEASUREMENT OF FLR VOLUME AND PREDICTING FUNCTION AFTER PVE

Computed tomography (CT) with volumetry is essential for planning hepatic resection (16,39,40). Three-dimensional CT volumetric measurements are acquired by outlining the hepatic segmental contours and calculating the volumes from the surface measurements from each slice (**Fig 1**). CT must be performed with intravenous contrast agent administration in several phases to demarcate the vascular landmarks of the hepatic segments. With this technique, the total liver volume and FLR volume can be calculated within minutes of scanning (40).

Two techniques of CT volumetry are commonly used. The first method measures the volume of the entire liver plus tumors and then the volumes of each measurable tumor. Total