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REVIEW ARTICLE

Portal Vein Embolization: What Do We Know?

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Abstract Portal vein embolization (PVE) has been developed to increase the size of the future remnant liver (FRL) left in place after major hepatectomy, thus reducing the risk of postoperative liver insufficiency. PVE consist in embolizing preoperatively portal branches of the segments that will be resected. Indication is based on preoperative measurements of the FRL by computed tomography and its ratio with either the theoretical liver volume or by direct measurement of the functional liver volume. After PVE, the volume and function of the FRL increases in 3 to 6 weeks, permitting extensive resections in patients otherwise contraindicated for liver resection. The PVE technique is variable from one center to another; however *n*-butyl-cyano-acrylate provides an interesting compromise between hypertrophy rate and procedure risk.

Keywords Embolization · Embolotherapy · Interventional oncology · Portal vein

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Introduction

Surgical resection of hepatic tumors is often the only curative option in primary and secondary liver tumors that may give patients a chance of long-term survival. However, the disease of many patients is considered unresectable because of an insufficient future remnant liver (FRL) volume to be left in place after extended surgical resection. The risk of liver failure after resection, as well as overall postoperative morbidity are directly linked to the volume of liver left in place by the surgeon [1]. In order to render more cases amenable to curative resection, portal vein embolization (PVE) is now an accepted technique to preoperatively increase the volume of the FRL.

PVE appeared in the late 1980s in Japan. In 1986, two publications opened the gate for the development of this technique. The first consisted of observations of hepatic lobar atrophy due to lobar portal invasion by cholangiocarcinoma [2]; the other consisted of a Japanese group's observations of atrophy of hepatic lobes in which they embolized portal branches in order to limit intraportal extension of hepatocellular carcinoma [3]. Simultaneously, they both noticed than segments with patent portal branches increased in size over time. These clinical observations confirmed the experimental results obtained by Rous and Larimore in the 1920s in a rabbit model of portal vein ligation [4]. The technique of PVE gained rapidly popularity in Japan in surgical groups treating hepatocellular carcinoma and Klatskin tumors [2, 3, 5, 6]. The first group that used PVE outside Japan was the Institut Gustave Roussy group in Villejuif, France, with Thierry de Baere as the interventional radiologist and Dominique Elias as the liver surgeon [7]. The first report in North America was that of David Madoff and Nicolas Vauthey from the MD Anderson Cancer Center in Houston, Texas, in 2000 [8].

Most liver surgeons have now endorsed this technique and use it in daily practice.

How Does PVE Work?

PVE is used in patient candidates who require extensive liver resection but have insufficient volume of FRL. Basically, PVE consist in occluding portal branches of segments that will be resected; the portal flow is then abruptly entirely redistributed toward the FRL's portal branches [9]. The mechanism of liver regeneration after PVE is a complex phenomenon that is not fully understood. From a histologic point of view, PVE induces atrophy of the embolized lobe as a result of both hepatocyte apoptosis and sinusoid dilatation, while in the nonembolized lobe, cells enter in an intense mitotic activity a few days after PVE, thus accounting for increased FRL volume after 2–4 weeks [10].

The biologic and cellular mechanisms of liver regeneration have been studied mainly in rodent models and in humans after extensive hepatectomy. From these publications, we know that hepatocytes that are usually quiescent in the G0 phase (only 1 out of 2000–3000 hepatocytes replicate in normal conditions) enter phase G1 one day after hepatectomy. Kupffer cells, endothelial cells, and bile duct cells replicate in a delayed fashion, suggesting that hepatocyte replication triggers proliferation of other cells [11]. After this initial phase of replication, hepatocytes increase progressively in size, allowing for gross liver growth [12]. Many molecular pathways are involved in liver regeneration after hepatectomy, such as tumor necrosis factor alpha, interleukin (IL) 6 produced by Kupffer cells, hepatocyte growth factor produced by stellate cells, vascular endothelial growth factor, and platelet-derived growth factor [13]. Platelets and serotonin have also demonstrated their crucial role in liver regeneration [14]. All these factors interact and overlap in their activities and roles. Regeneration after PVE is somewhat different in term of intensity, with lower production of IL-6, IL-1, and tumor necrosis factor alpha after embolization. Mechanisms of regeneration after PVE are also delayed compared to regeneration after hepatectomy [15].

A deeper understanding of the mechanism involved in liver regeneration is crucial to improve the results of PVE. The role of heat shock protein 70 (a protein involved in cell reparation mechanisms) has also been evaluated as inductor of liver regeneration in human [16]. Miyake et al. have shown an increase by two- or fourfold in the nonembolized liver compared to embolized liver after PVE. Interestingly, in their series, only one patient did not show increase of heat shock protein 70 after PVE and subsequently died of liver failure after hepatectomy. Some groups have even explored the potential of heat shock protein 70 inducer geranyl–geranyl–acetone to stimulate liver regeneration. Administration of geranyl–geranyl–acetone increases tolerance to major hepatectomy but has never been tested in combination to PVE [17].

Despite many interesting animal and experimental studies, the trigger of liver regeneration after PVE remains unknown. The players are similar to those after hepatectomy, but the initial phenomenon remains mysterious. Is it a vascular stress in the FRL induced by abrupt portal redistribution, or is it in the embolized liver that the process is initiated by periportal inflammation? They remain open questions. It is noteworthy that different studies identified periportal inflammation in the embolized lobe from pathologic studies as an important predictor of liver regeneration, both in human and experimental animal studies [18, 19].

How Are Patients Selected for PVE?

Selection of patients for PVE is decided during multidisciplinary meetings and by tumor boards. The decision directly depends on the planning of the surgery, the amount of liver to be resected, and the functional status of the liver. This risk is related to the volume of liver left in place after surgery, to the function of the parenchyma (cirrhotic, cholestatic, fibrotic, steatotic) [12], and to the complexity of surgery that will prolong liver ischemia periods by vessel clamping and will increase intraoperative blood loss, and consequently will further increase risk of postoperative liver failure. Therefore, selection for PVE is based on three factors: liver volumetry as assessed by computed tomography (CT), liver function test, and resection complexity. Such ambitious surgical multistep projects are usually proposed to motivated patients in good general condition.

The first factor is easily established by means of CT after injection of contrast media. Attention should be paid to having a sufficient enhancement of both portal branches and hepatic veins to precisely delimit liver segments. Volumes are then delineated by manually tracking the limits of segments and tumors and automatically calculating volumes from axial slices. Recently, automatic recognition of liver segments allowing for "automatic volumetry" have become available from some companies [20].

Different methods have been used to determine the ratio between the FRL and the total functional liver volume (FLR ratio). Differences are related to the definition of total FLR. Some authors use direct measurement of the total liver volume minus tumor volume by CT [21–23]. Others use a standardized evaluation of the normal liver volume in white subjects on the basis of a formula using the formula body surface area (total liver volume (cm^3) = − 794.41 + 1267.28 × body surface area (m^2)) [24]. The last method is to express this ratio

as a percentage of body weight [25, 26]. Shah et al. [25], comparing these three ways to estimate the FLR ratio, found that the best method to estimate the risk of postoperative liver failure was the formula estimating liver volume from body surface area described by Vauthey et al. [24]. The situation is probably different in diseased or cirrhotic liver, but to our knowledge, this has not been evaluated. In such conditions, comparison of the FLR ratio threshold between one publication and another becomes complex and not very feasible (Table 1). The consequence is that some groups, for patients with normal liver, use a FLR threshold at 30% and others at 20% to decide PVE [26, 27].

Evaluation of liver function is more complex and debated. Patients with cirrhosis have been extensively studied in that regard, while patients treated by chemotherapy or with steatotic livers have been less studied. In patients with cirrhosis, estimation of hepatectomy risk is a conjunction of three elements: Child-Pugh score, measurement of portal hypertension, and, in some groups, indocyanine green (ICG) test. The latter evaluates both global liver perfusion and biliary excretion by measuring the extraction from the serum by the liver of ICG that is excreted unchanged into the bile. An ICG retention rate of >20% at 15 min is considered to be a contraindication for resection [28]. Portal hypertension can be estimated by direct measurement of hepatic vein pressure gradients, by oesogastric endoscopy, or by imaging identification of large porto–caval collaterals [29, 30]. Selection criteria for other patients at high surgical risk are less established. For instance, there is no universally accepted way to select in patients treated by multiple courses of chemotherapy or with metabolic syndrome and steatosis [31, 32].

Table 1 Schematic description of the advantages and disadvantages of ipsilateral and contralateral approaches for PVE

Pros and cons	Contralateral	Ipsilateral
Pros	Catheterism easier	No risk for FRL
	Final control portography easier	Easy puncture as a result of larger portal branches
	Use of NBCA	Access to segment 4 branches
Cons	Risk of complications in the FRL	Catheterism of right portal branches more complex
	(increased by portal hypertension)	Use of NBCA more tricky
		Final control hard to achieve is NBCA used
		Risk of tumor seeding
		Risk of liver infarction in case of arterial complication during access

Performing PVE in every patient before major resection does not influence postoperative morbidity and mortality [33]. The usual threshold accepted by most of the surgical teams is as follows. In young patients with a normal liver and without risk factors for liver surgery, a hepatectomy removing 75–80% of the functional liver is acceptable. In cirrhotic Child A patients with a portocaval gradient under 12 mm Hg, removing more than 60% of the liver volume is considered to put the patient at risk of postoperative liver failure. In patients with multiple courses of chemotherapy, steatosis, and cholestatic liver, and a FRL to total liver ratio of 20–40%, the decision is made on an individual, basis taking all risk factors into consideration. A very small left lobe (under 10%) should not be considered a contraindication; two recent studies have demonstrated in metastatic patients and in cirrhotic patients that there is a correlation between small initial size of the FLR and high degree of hypertrophy [23, 34]. In other words, the smaller the left lobe, the greater its hypertrophy after PVE.

Should We Evaluate Liver Volumes or Liver Volume and Function by Nuclear Medicine?

Over the last few decades, scintigraphic techniques have been used for noninvasive, direct evaluation of liver function and have several benefits over the more established, indirect method using CT volumetry [35].

^{99m}Tc-galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy measures the binding of asialoglycoproteins on its receptor, which is expressed only on the sinusoidal surface juxtaposing the Disse space of the mammalian hepatocytes [36]. The receptor is involved in the endocytosis of the asialoglycoproteins subsequently degraded by lysozymes. Over last few decades, several indices of liver function have been developed in planar scintigraphy and single-photon emission computed tomography (SPECT) [35]. They show a good correlation with conventional liver function tests, ICG clearance test, Child-Pugh classification, and histology (hepatic index activity score). In 9–17% of patients, there is a discrepancy between ICG clearance testing and ^{99m}Tc-GSA scintigraphy; the latter better reflects the histologic severity of liver function [37, 38] and is not parasitized by hyperbilirubinemia.

Moreover, it is an independent predictor of postoperative complications, in contrast to ICG. Concerning PVE, ^{99m}Tc-GSA SPECT scintigraphy demonstrated additional value over CT volumetry for evaluating functional increase after PVE [39–41], by demonstrating a higher increase in function of the nonembolized liver by ^{99m}Tc-GSA SPECT/CT than by CT-volumetry (+21.4% vs. +13.9%, $P < 0.001$). In a similar study using ^{99m}Tc-GSA SPECT/CT, criteria could be proposed on the basis of total amount

of receptor in the remnant liver to select candidates for PVE with good clinical outcome and thus expand the range of hepatic resection [42]. Unfortunately, the ^{99m}Tc-GSA kit is only commercially available in Japan and is not currently available for use in Europe or the United States (Fig. 1).

The ^{99m}Tc-iminodiacetic acid (^{99m}Tc-IDA) derivative scintigraphy has been used for more than three decades for hepatobiliary scintigraphy. These lidocaine analogs are transported to the liver mainly bound to albumin, where it is cleaved in the Disse space. From there, ^{99m}Tc-IDA compounds enter the basal membrane of the hepatocyte through anion transporters before being excreted unmetabolized to the biliary tract [43]—similar to ICG—by the ATP-dependent export pump multidrug-associated protein 2. As these agents follow a path similar to bilirubin or toxins, they have been proposed as an index of liver function [44]. Of all available IDA derivatives, ^{99m}Tc-mebrofenin is the agent of choice, with high hepatic uptake, minimal urinary excretion, and resistance to high levels of bilirubinemia. Hybrid SPECT/CT acquisitions have been used to derive regional liver function around the peak of the hepatic time–activity curve, allowing calculation of remnant liver function on the basis of contouring the liver outline via low-dose CT [45].

^{99m}Tc-mebrofenin scintigraphy has been validated in the preoperative assessment of liver function [46, 47], with a good correlation with ICG testing [48]. The combination of dynamic hepatobiliary scintigraphy and SPECT to morphologic volume measured by CT was able to accurately predict actual postoperative liver function of the remnant liver [45]. This technique is currently applied to measure the regional increase in liver function after PVE. ^{99m}Tc-mebrofenin scintigraphy could be used to select patients for PVE thanks to its demonstrated ability to predict increased postoperative liver failure [49]. A step in this direction was taken using hypothetical values for safe resection in function and volume increase after PVE. De Graaf et al. [50] showed that the increase in function as measured by ^{99m}Tc-mebrofenin was larger than the increase in volume. This suggests that the waiting time until resection may be shorter than the 3–4 weeks indicated by volume expansion. Thus, some authors advocate that function-based criteria, in addition to volume-based criteria, should be used, especially when liver resection needs to be performed with minimal accepted remnant volume [51].

How Is PVE Performed?

The technique of PVE is extremely variable from one center to another, depending on operator preference (Table 1). The access route can be ipsilateral or contralateral. Some authors use the ipsilateral approach, puncturing a right portal branch and embolizing in a retrograde fashion all right portal branches. This access allows for an easy catheterization of segment 4 branches when they must be embolized. The drawback of this technique is mainly the difficulty of access to the right portal branches in a retrograde fashion, and also sometimes the difficulty of finding a route through healthy liver to the right portal branches [6, 52]. The contralateral approach aims to puncture a left peripheral portal branch (Fig. 1). Catheterization of the right portal branches is theoretically easier, if anatomy is standard. Such contralateral access renders final control portography easier because the catheter does not have to pass through embolic material to be placed in the portal vein for final contrast injection [7, 23, 53]. Choosing the access also depends on the embolic material used. Glue can hardly be manipulated from the ipsilateral side, while large embolic materials, like plugs, need large-diameter access, which is less risky when obtained on the ipsilateral side [54]. The final choice between the ipsilateral and contralateral routes should be made by comparing their respective complication rates. They seem similar and are mainly related to puncture of unexpected structures, such as biliary branches or hepatic arteries. The largest series of contralateral PVE reviewed 188 cases at different centers using contralateral access and *n*-butyl-cyanoacrylate as an embolic material [55]. Only six of the 12 reported

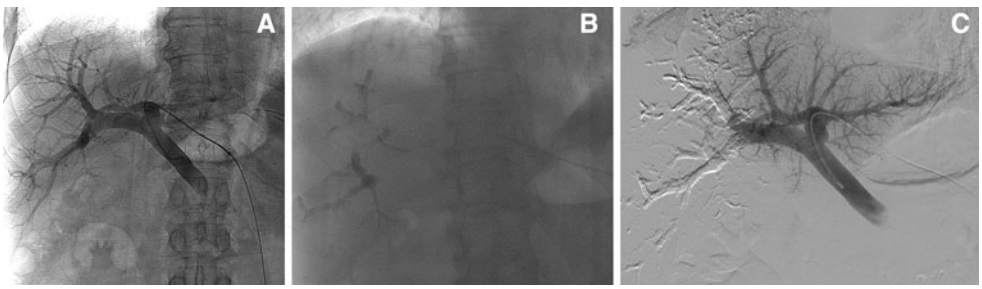

Fig. 1 A 67-year-old man bearing four liver metastases in the right lobe. The decision was made to perform PVE before right hemihepatectomy. **A** Segment 3 branch and portography in the right anterior oblique view were obtained. **B** The right portal branches were embolized with a mixture of NBCA and ethiodized oil. **C** Subtracted portography after PVE showing complete redistribution toward the left lobe. Parenchymatous enhancement was only evident on the right side

complications could be related to the access route, but none precluded liver resection. It is also interesting to note that these complications mainly occurred in patients with portal hypertension. Another series reported similar rate of complications using the ipsilateral route [56]. Finally, arterial or biliary complications do not have the same consequences if the portal vein is occluded or patent. Embolization of a traumatized hepatic arterial branch may lead to infarction on the ipsilateral side of PVE and have no impact on the contralateral side. Our policy for right PVE using n-butyl-cyano-acrylate (NBCA) is to use the contralateral side. We use the ipsilateral side when segment 4 branches must be embolized and when the left lobe is quite small and barely accessible. Other access routes have been described through surgical dissection and catheterization of the ileocolic vein. This access has the benefit of not puncturing the liver, but it makes the procedure more complex and catheter manipulation trickier [57].

Our recommendation and habit is to use the contralateral access route and to embolize with NBCA mixed with lipiodol. The risk of local complication is low and can be managed without difficulty because the portal flow is opened on this side (Fig. 1).

Which Embolic Material Should Be Used?

Various embolic materials have been used for PVE, including Gelfoam [7], NBCA [23], different types and size of beads [58, 59], alcohol [60], and nitinol plugs [54] (Table 2). All of these embolic materials are able to occlude the right portal branches and redistribute flow toward the FRL. There is no official recommendation for a specific embolic material [61]. There is no single-center comparative study evaluating which embolic material provide better hypertrophy, and comparison between series are not helpful because these series have neither standardized inclusion criteria nor standardized delay after PVE for CT evaluation of hypertrophy (2–6 weeks). In addition, the rate of hypertrophy after PVE depends on the preembolization FRL volume more than any other factor, as described previously [34].

However, the choice of the embolic material can be influenced by the results of experimental studies. Recently, De Baere et al. have compared in a pig model three commercially available embolic materials: NBCA mixed with iodized oil, and two different sizes of spherical particles. NBCA seemed to be more efficient in including liver regeneration than spherical particles. A correlation of periportal fibrosis in the embolized lobe and liver regeneration was also found [19]. This result is in concordance with previous observations in human. If particles are used, more significant hypertrophy is obtained with small-size spherical particles compared to larger-size or nonspherical particles [62].

Should PVE or Surgical Ligation of the Right Portal Branches Be Performed?

Surgical ligation of the right portal branches is an invasive surgical procedure requiring dissection of the liver hilum during a laparotomy. Controversy exists about the respective indications of PVE and ligation. Portal vein ligation seems efficient to induce left lobe hypertrophy [63, 64], but because of its invasiveness, it is mainly used in the so-called two-stage hepatectomy [65]. Patients with bilobar metastases are operated on for resection of left lobe metastases, and right portal vein ligation is achieved in the same procedure. Four to 5 weeks thereafter, the left liver has increased in size, and right hepatectomy can be performed. However, portal vein ligation does not occlude distal portal branches; the development of multiple intrahepatic porto–portal collaterals—namely from segment 4 to segments 5 and 8—is possible [66]. Even if portal vein ligation allows for a two-stage hepatectomy, another option in bilobar disease with small-size tumor in the left is radiofrequency ablation of the left liver metastases and PVE in the same procedure [67], followed 4 weeks later by right hemihepatectomy.

Animal studies have conflicting results comparing regeneration rate after portal vein ligation or embolization. Studies in rats demonstrated superiority of ligation [68], while more recent studies have shown the opposite in larger animals (pigs and rabbits) [69, 70]. The explanation might be that the liver in rodents are almost foliated with separated liver segments, while in pigs and in rabbits intrahepatic porto–portal collaterals developed, thus probably limiting the occlusive effect of ligation. Furthermore, hilar dissection in rats is probably associated by arterial lesions in the ligated segments, increasing the effect of portal ligation.

Should Segment 4 Branches Be Embolized?

In a prospective study analyzing liver volumes in a normal population [71], volumes of segments 2 and 3 have shown to account for less than 20% of the total liver volume in nearly 80% of the population. In other words, PVE should be performed in 80% of the cases when an extended right hepatectomy has to be performed. The question is in these cases is, should we or should we not embolize segment 4 branches? The results described in the literature are controversial. Two elements should be kept in mind when evaluating patients for segment 4 embolization. First, the procedure is much more complex and can hardly performed from the contralateral approach. This implies that NBCA will probably not be used, and that a very careful embolization will be performed on these branches with

Table 2 Results of main PVE studies

Study	No. of patients	HCC/LM/CCC/GBC/other	Embolic agent	PTPE access (ipsilateral/contralateral)[a]	Estimation of FLR/TELV ratio[b]	FLR change (%)/increase FLR/TELV (%)
Okabe et al. 2011 [84]	19	19/0/0/0/0	NR	19/0	1	17.2/NR
De Graaf et al. 2011 [50]	24	0/14/5/1/4	MS	23/1	1,2	8.5/NR
De Baere et al. 2010. [34]	107	0/97/7/3/0	NBCA, IO, MS, C	106/1	1	69/13
Palavecino et al. 2009 [85]	21	21/0/0/0/0	MS, C	21/0	1,2	NR
Yoo et al. 2009 [86]	41	16/2/19/0/4	AGS, VP	38/3	1	25.4/7
Yokoyama et al. 2008 [87]	88	0/0/52/36/0	Fg, IO, E, C	88/0	1,2	NR/21 in men and 23 in women
Giraudo et al. 2008 [88]	146	10/111/19/6/0	NBCA, IO	0/146	1	48/NR
Ribero et al. 2007 [73]	112	24/65/14/6/3	NR	NR	1,2	NR/8.8 in patients with cirrhosis, 10.9 without cirrhosis
Denys et al. 2005 [23]	40	40/0/0/0/0	NBCA, IO	40/0	1	41/NR
Covey et al. 2005 [58]	58	0/58/0/0/0	MS	52/6	1	24.3–31.9/9–10
Sugawara et al. 2002 [89]	66	66/0/0/0/0	AGS, DSM, G, Thr	PTPE, 25 patients (ipsilateral vs. contralateral NR); TIPE, 41 patients	1	47%/NR
Wakabayashi et al. 2002 [90]	43	25/10/8/0/0	AGS	NR	1	34% Normal liver, 25% chronic liver disease/NR
Azoulay et al. 2000 [91]	30	0/30/0/0/0	NBCA, IO	1 Ipsilateral/29 contralateral	1	NR/11
Imamura et al. 1999 [92]	84	5/7/49/22/1	AGS, Thr, DSM, IO, G	PTPE,:6 patients (ipsilateral. vs. contralateral NR); TIPE, 78 patients	1	30.7/10.2

HCC hepatocellular carcinoma, *LM* liver metastasis, *CCC* cholangiocarcinoma, *GBC* gallbladder carcinoma, *NR* not reported, *FLR* future liver remnant, *TELV* total estimated liver volume, *C* coils, *MS* microparticles, *AGS* absorbable gelatin sponge, *Fg* fibrin glue, *E* ethanol, *VP* vascular plug, *NBCA* n-butyl 2-cyanoacrylate, *IO* iodized oil, *DSM* diatrizoate sodium meglumine (Urografin), *G* gentamicin, *Thr* thrombin, *PTPE* percutaneous transhepatic route, *TIPE* transileocolic route

[a] Ipsilateral approach (access through the portion of the liver to be resected) is recommended so as to not injure the FLR. Route is PTPE vs. TIPE; the latter is performed by surgeons at open laparotomy with direct cannulation of the ileocolic vein

[b] Estimation of FLR/TELV ratio is as a direct measurement by CT; as a standardized evaluation of the normal liver volume based on a formula using body surface area; or as a standardized evaluation of the normal liver volume based on a formula using the body weight

particles and coils. This also means that the surgeon will have to resect segment 4 in toto, which is rarely the case in clinical practice. Because segment 4 has multiple portal branches, it can also be resected incompletely, leaving more parenchyma postoperatively.

Madoff et al. initially reported that embolization of segment 4 branches nearly double the rate of hypertrophy of the left lobe [62]. These results have not been found in other experienced centers, which have even observed the contrary [34, 72]. These groups observed maintained hypertrophy of segment 4 after embolization of segment 4 branches. They suggested that segment 4 portal-branch embolization is rarely complete, and that persistent patent segment 4 portal branches account for maintained regeneration.

What Should Be Done If Hypertrophy Is Insufficient after PVE?

This situation is more frequent when considering patients with chronic liver disease. Indeed, in a retrospective analysis of 42 consecutive cases, we observed nearly 10% of patients without significant hypertrophy after PVE [23]. These patients were not operated on because insufficient hypertrophy after PVE is usually considered a risk factor for liver insufficiency after PVE. For some authors, a degree of hypertrophy estimated as a percentage of increase of the FRL below 10% in patients having chronic liver disease is an indication of high risk of liver insufficiency [33]; the same was observed with a degree of hypertrophy of 5% for patients with normal liver [73]. Associated risk factors for liver insufficiency in patients after hepatectomy prepared by PVE are associated jaundice and extensive dissection of the hepaticoduodenal ligament [74].

In cases of patients with chronic liver disease, it may be necessary to wait longer (6–8 weeks after PVE) to obtain sufficient hypertrophy. A recent study has demonstrated that hypertrophy and regeneration may continue over a 1-year period after PVE [75].

Can We Predict Liver Regeneration after PVE?

There is no way to predict hypertrophy after PVE. Many factors have been identified and influence regeneration. However, the most significant factor is the size of the FRL before PVE [23, 34], in cases of both healthy liver and chronic liver disease. This means that surgeons and interventionalist should not preclude PVE in case of very small left liver volumes, but on the contrary expect marked hypertrophy in these cases. Indeed, PVE was able to provide enough hypertrophy to convert the patient to surgery with a FRL as low as 6.9%, which clearly open the gate for resection of all the liver except one segment—a notion that to our knowledge has never been explored. Other factors identified as decreasing the rate of regeneration must be kept in mind, and in these cases, PVE can be considered as a test for the capacity of the liver to regenerate. Factors known to negatively influence regeneration include diabetes, liver fibrosis F4, cholestasis, and portal hypertension. Other factors are known to have no influence on liver regeneration, including sex age, origin of the tumor, chemotherapy with anti–vascular endothelial growth factor such as bevacizumab, and ICG clearance [76]. Chemotherapy with oxaliplatin may induce severe sinusoidal obstruction and subsequent portal hypertension, making PVE more difficult and potentially more at risk of complications [77] (Fig. 2).

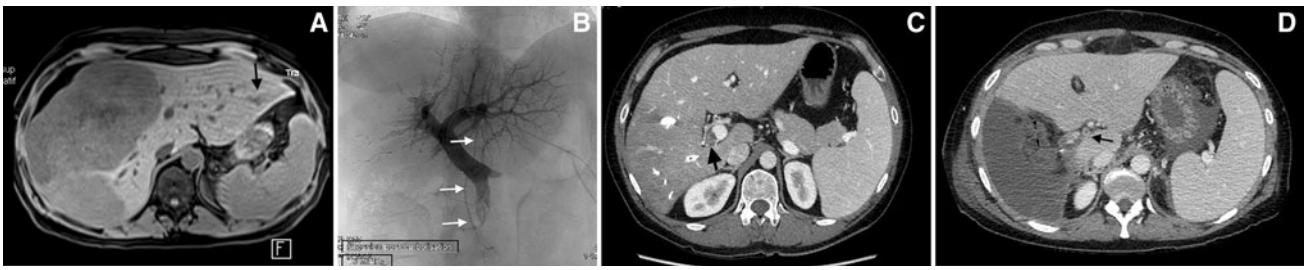

Fig. 2 A 45-year-old woman treated with six cycles of chemotherapy with oxaliplatin, 5-fluorouracil, and folinic acid. Because of the presence of stable disease, right hepatectomy was chosen. Because FRL ratio is 28%, and taking into account the percutaneous destruction of a small segment 3 lesion, a right PVE was performed. **A** T1-weighted axial image identifying both right hepatic lobe metastases and small nodular lesion in segment 3 (*arrow*). **B** After PVE, portography confirmed occlusion of right portal branches, and the hepatofugal paraumbilical vein was identified (*white arrows*). **C** A control CT was performed 1 month after PVE, revealing partial thrombosis of the portal vein trunk (*arrow*), while segments 2, 3, and 4 increased in size. **D** During hepatectomy, right portal vein ligation was made more complex by portal vein thrombosis and stenosis of the portal vein associated with portal hypertension after hepatectomy induced complete portal vein thrombosis at postoperative CT (*arrow*)

Is Surgery More Complex after PVE?

Complications after PVE should not be underestimated and may impair future surgery. Hematoma, hemobilia, and sepsis, as well as embolization material going to the non-embolized lobe, resulting in partial or complete portal vein thrombosis, are rare but may be serious problems for surgery [34]. For surgical strategy in cases of hilar cholangiocarcinoma, it is important to preoperatively precisely determine the liver side to be embolized and resected. It is obvious that once the PVE is performed, an intraoperative change in the resection strategy is no longer possible, thus making a preoperative precise diagnosis mandatory before PVE [78].

Even without PVE-induced complications, postoperative complications of major liver surgery after PVE are increased, with a clear trend for higher intraoperative bleeding from the dilated intrahepatic venous collateral [34, 79–81].

In fact, operation duration after PVE is significantly longer, and there is increased blood loss. The postoperative complication rate after PVE is about 40%, with mortality at 30, 60, and 90 days of 2%, 4.7%, and 6%, respectively [81]. This increased morbidity and blood loss are due in part to more complex resection, but also to the above-mentioned dilated collateral veins after PVE. The important point is that blood loss has been correlated with impaired postoperative liver regeneration in an experimental model [82]. This is correlated with clinical studies that reveal blood transfusion to be an independent predictive factor for postoperative liver insufficiency [81, 83].

Major postoperative changes in portal blood flow after PVE followed by extensive liver resection are observed. The volume of portal blood flow may increase up to threefold and may lead to a relative venous outflow block and liver congestions, thus forming a small-for-size liver [78].

Conclusion

PVE is a well-established technique. It is now used worldwide to enhance patient safety after major hepatectomy. This technique is probably still in its infancy; regeneration enhancers, safer embolic material, association to hepatic vein embolization are many new ways that will permit more aggressive surgical options. Removing all the liver except for one segment is still a utopian ideal—but probably not for long.

Conflict of interest The authors declare that they have no conflict of interest.

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