Clinical and experimental studies on portal vein embolization / Diagnosis of hepatocellular adenoma and focal nodular hyperplasia
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Controversies in the use of portal vein embolization

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Abstract

Background: Portal vein embolization (PVE) has reached worldwide acceptance to increase future remnant liver (FRL) volume before undertaking major liver resection. The aim of this overview is to point out and discuss current controversies in the application of PVE.

Methods: Review of literature pertaining to techniques of PVE, complications, tumor proliferation, timing of resection, and hypertrophy response after PVE.

Results: Procedure-related complications after PVE include hematoma, hemobilia, overflow of embolization material, and thrombosis of portal vein branch(es) of the non-embolized lobe. Persistence of the embolized, atrophic lobe is usually not harmful. Embolization of the portal branches to segment 4 in addition to embolization of the right portal trunk is controversial and is advised only in selected cases. It remains undecided whether embolization of the portal venous system is more effective in inducing hypertrophy of the FRL than ligation of the portal vein. Accelerated tumor growth after PVE is a major concern and requires consideration of post-PVE chemotherapy. A waiting time of 3 weeks between PVE and liver resection is advised. Post-hepatectomy regeneration is not hampered after preoperative PVE.

Conclusion: PVE is a useful preoperative intervention to increase volume and function of the FRL. Further progress awaits clarification of the mechanisms of the hypertrophy response induced by PVE in conjunction with new embolization materials and protective chemotherapy.
Introduction

Preoperative portal vein embolization (PVE) has become a well-established means to upsize the future remnant liver (FRL) in patients considered for extensive liver resection.\(^1\) Although the concept of portal vein occlusion inducing the liver atrophy-hypertrophy complex was described previously in experimental studies, Makuuchi was the first to perform preoperative PVE clinically. His first patient in whom PVE was carried out had a hilar cholangiocarcinoma requiring extended liver resection.\(^2\,^3\) Obviously, this was a serendipitous action because a substantial proportion of patients with hilar cholangiocarcinoma present with unilateral portal vein occlusion and a marked atrophy of the affected, ipsilateral side of the liver, while hypertrophy of the contralateral side may be impressive. Instead of the tumor blocking the portal vein branch, the same effect can be achieved using an intervention by which the portal vein branch is occluded. Although PVE now is a widely used interventional procedure to improve the outcome of major liver resection, there are still several controversies and issues which are addressed herein.

**Do we really need portal vein embolization?**

Although most centers now use PVE, the criteria for preoperative application of PVE are not well defined. PVE is considered when the FRL is found to be too small for sufficient postoperative function. In livers with normal parenchyma as is usually the case in patients with liver metastases, the minimum volume of remnant liver may be 25% based on CT volumetric studies to avoid post-resection liver failure. However, when there is liver parenchymal disease such as in cirrhosis, the minimum volume of remnant liver is rather set at 40 or even 50% depending on liver functional reserve. In a prospective clinical trial from the group of Beaujon Hospital in Paris, patients undergoing standard right hemihepatectomy were randomized to receive preoperative PVE or not.\(^4\) In patients with normal liver, the hypertrophy of the FRL induced by PVE had no beneficial effect on the postoperative course. However, in patients with chronic liver disease, the rate of postoperative complications was significantly reduced after preoperative PVE. These results suggest that PVE is particularly advantageous in patients requiring extended liver resection or in patients with diseased livers. There are also series of partial liver resection in literature showing excellent results of liver resection without using PVE, such as the series published by the Memorial Sloan Kettering group in New York reporting a mixed series of 1,803 patients undergoing partial liver resection.\(^5\) This series included patients with cirrhosis and showed an overall mortality of 3.1% and morbidity of 45%. Hence, as long as the true minimum volume of liver required for safe resection in a normal liver is debatable, the indication for performing PVE in normal livers remains controversial. On the other hand, in patients with normal liver requiring liver resection associated with a major gastrointestinal procedure, PVE is recommended.\(^6\) There is little discussion,
however, that in patients with chronic liver disease or injured livers as a result of cholestasis, steatosis or after chemotherapy, preoperative PVE should be considered to improve the safety of any substantial liver resection.

What are the disadvantages of PVE?

When evaluating a patient for major liver resection in whom the future remnant liver is calculated to be marginal, one may tend to stay on the safe side and apply preoperative PVE. Although PVE is considered a safe procedure, a recent meta-analysis of 1,088 patients who had successfully undergone PVE showed an overall morbidity rate of 2.2%, however, with no mortality. Complications reported due to the procedure are hematoma, hemobilia, septic complications, backflow of embolization material and thrombosis of the main portal vein or branch(es) of the portal venous system to the liver segments to be preserved. Obviously, the latter complication has important consequences for the resection plan, oftentimes rendering the patient technically unresectable. From an oncological point of view, enhancement of tumor cell proliferation in both the embolized and nonembolized lobes in the time after PVE are a concern, as addressed below in this overview.

Another uncertainty is the fate of the embolized liver segments when resection is not carried out because of tumor progression or extrahepatic metastases found at laparotomy. In the authors’ experience, there are no long-term adverse effects of the persisting embolized lobe in the presence of the nonembolized lobe, inasmuch as the atrophy-hypertrophy complex stabilizes and overall liver function is maintained. The situation is different, however, in patients with resectable hilar cholangiocarcinoma.

These tumors typically require hilar resection with en bloc extended liver resection including the caudate lobe to achieve a R0 resection. Remnant liver volume is particularly critical in these patients because of concomitant cholestasis even when the biliary system on the side of the future remnant liver segments, usually segments 2 and 3, is adequately drained. In these patients, the remnant liver volume ideally is 35-40% often necessitating patients to undergo PVE in order to achieve this volume preoperatively. PVE, however, predetermines the side of the liver to be resected. This situation cannot be changed when on the basis of intraoperative findings during exploration, the resection strategy is reconsidered and the surgical approach is decided to be from the opposite side. Resecting the nonembolized liver and leaving the embolized, atrophic liver, is, of course, not an option. Even when the patient is found to be unresectable, persistence of the embolized liver segments may generate serious problems because the affected bile ducts are usually infected and incompletely drained. These liver segments are prone to develop troublesome abscesses after PVE, while the tumor progresses and additionally occludes the ipsilateral hepatic artery (Figure 1). Under these circumstances, the need for a palliative liver resection may be considered during explorative laparotomy.
Figure 1. Patient with hilar cholangiocarcinoma who had undergone preoperative transhepatic biliary drainage and subsequent PVE was found to be unresectable during exploratory laparotomy. Persistence of the embolized liver segments in combination with progressive obstruction of infected bile ducts resulted in troublesome liver abscesses requiring percutaneous drainage. A: CT scan showing atrophied right liver lobe with internal biliary, metal stents (white arrow) and intraportal coils (white circle). B: Drainogram showing abscess in continuity with biliary tree.

What is the most effective technique: portal vein ligation or embolization?

The first question that arises is: What is the most effective method to interrupt portal perfusion of the part of the liver to be resected? Basically, the two modalities are ligation of the portal vein (PVL) or embolization of the portal venous system (PVE), usually of the right hemiliver. Ligation of the right portal vein is performed during laparotomy, when the left FRL is considered too small, or in a two-stage procedure, in which part of the resection on the left side is undertaken with concomitant ligation of the right portal vein, followed by a second resection (right hemihepatectomy) to complete the procedure after regeneration has taken place. Portal vein ligation in this setting is carried out by the surgeon during laparotomy. The surgeon can also choose to cannulate the ileocolic vein and pass a balloon catheter into the right portal venous trunk and embolize the portal system with particles or fibrin glue under fluoroscopic guidance.

Alternatively, absolute alcohol can be injected into the right portal vein as a sclerosing agent prior to ligation, with the aim of obliterating the portal venous system in addition to occluding its origin. This combination, however, is reported to be accompanied by fibrosis and severe pain and, therefore, is not used very often anymore. In most centers, nowadays, PVE is performed using the percutaneous, transhepatic approach under local anesthesia. This procedure is undertaken by the interventional radiologist under ultrasound and fluoroscopic guidance. The transhepatic approach obviously requires expertise of an interventional radiologist dedicated to HPB procedures. Access to the portal venous system using the transhepatic approach is obtained either via the contralateral route or via the ipsilateral route. Although the ipsilateral route is technically more demanding, the advantage of this approach is the lower risk of injury or thrombosis of the portal vessels of the future remnant liver.

A survey in The Netherlands showed that in...
2006 and 2007, 98 occlusions of the portal vein were performed. Approximately half of the procedures (48/98) were carried out as PVL, whereas the other half underwent transhepatic PVE (50/98). This reflects the initial, relative lack of radiologists being able to perform the procedure, while experience is now expanding and transhepatic PVE has become available in many of the specialized centers.

Intuitively, one would consider PVE more effective because it occludes the entire portal tree on the embolized side, whereas with PVL, only the entry of the portal venous trunk is occluded. A patent portal system distal to the site of ligation would easily enable collateral perfusion from the adjacent, nonocluded liver segment(s) resulting in retrograde filling of the ipsilateral portal veins. In support of this hypothesis, Wilms et al. from Kiel applied PVE and PVL in a pig model and concluded that PVE was the more effective technique to increase the future liver remnant, owing to more durable occlusion of the portal venous branches. The short-range occlusion achieved by PVL resulted in retrograde filling of the portal system, most probably by arterial-portal connections located in the same liver lobes. However, recent (experimental) data show that this is still a controversial issue. In a retrospective clinical study from the group of Beaujon Hospital in Paris, Aussilhou et al. reported that right PVL was as effective as PVE to induce hypertrophy of the left liver remnant. However, in this study, PVL was undertaken in the setting of a two-stage liver resection. The combination of PVL with partial liver resection introduces an advantage because of postsurgical liver regeneration augmenting post-PVL regeneration. In contrast, using a rat model of selective PVE or PVL, Furrer et al. from Zurich elegantly showed that hepatocyte proliferation after PVL was more pronounced than after PVE, suggesting that PVL is the more effective technique. The regenerative response after PVE was possibly hampered by a massive foreign body reaction around the microspheres used for embolization, draining the macrophages which are instrumental in starting hepatocyte proliferation in the non-embolized lobes. As long as the (patho)physiological events governing post-PVE or post-PVL regeneration are unclear, it is difficult to attest which is the superior technique. Percutaneous PVE obviously is a less invasive procedure than PVL requiring a laparotomy. However, reports are accumulating in which PVL is undertaken laparoscopically, hence combining a staging procedure with PVL in one minimally invasive session.

Is embolization of the segment 4 portal branches advised in extended right hemihepatectomy?

Controversy exists concerning embolization of the portal branches to segment 4 in preparation of extended right hemihepatectomy in addition to embolization of the right portal trunk. Access to the portal tributaries to segment 4 has to be gained via the portal bifurcation and/or left portal trunk, increasing the risk of injuring the left portal vein. Another potential mishap is the backflow of embolization material into the left portal venous system leading to inadvertent embolization and thrombosis.
of the portal vessels of the FRL. In our experience, this complication occurred in one patient who, in spite of thrombectomy during exploration, was eventually considered too high risk for resection (Figure 2). Although Ribero et al.\textsuperscript{12} reported no difference in the incidence of complications after right PVE + segment 4 and right PVE alone, selective embolization of the portal branches to segment 4 is considered a difficult extension of PVE, obviously requiring an expert interventional radiologist. Even in experienced hands, partial embolization of the segment 4 portal branches may be preferred (only the branches to segment 4a) above embolization of the whole segment. A surgical approach encompassing PVL and selective ligation of the portal branches to segment 4 and segment 9 (and even to segment 1) may seem more secure, but has the disadvantage of scarring the hilar area which makes subsequent dissection at the time of resection more difficult. In case of tumor deposits in segment 4, as is usually the case when an extended right hemihepatectomy is elected, incomplete embolization of segment 4 carries the risk of stimulating tumor growth in the nonembolized areas, thus creating a dilemma.

Figure 2. CT scan of patient with hilar cholangiocarcinoma who had undergone preoperative PVE in anticipation of extended right hemihepatectomy. Embolization of the right portal trunk and the portal branches to segment 4 resulted in backflow of embolization material into the left portal venous system and partial thrombosis (black arrow) of the left portal vein. White circle is drawn around the intrportal coils.

Is tumor growth accelerated after PVE?
Potential promotion of tumor growth after preoperative PVE and consequent acceleration of tumor progression in the waiting time until resection are a major concern possibly limiting the use of PVE in patients with multiple liver metastases. This is an area of debate which has recently been extensively reviewed by de Graaf et al.\textsuperscript{13} Several authors reported increased proliferative activity of colorectal liver metastasis following PVE.\textsuperscript{14-16} Clinical evidence is, however, based on studies with small sample size. Kokudo et al.\textsuperscript{14} published the largest case series in which 19 patients undergoing PVE were compared to 29 patients resected without PVE (controls). Mean tumor volume, measured by CT volumetry, had significantly increased by 20.8% in
the 3-week interval after PVE. The proliferation rate of metastatic lesions which was based on histological assessment (Ki-67 labeling index) was significantly higher in the PVE group than in the control group undergoing only resection. Tumor progression precluding curative resection has been associated with rates ranging from 6.4 up to 33%. A recent meta-analysis reported that 11.3% of the 85% of the evaluable patients that had undergone PVE and subsequent exploratory laparotomy were unresectable due to intra- or extrahepatic tumor spread.13,17

Three important mechanisms influencing tumor growth after PVE have been recognized, i.e. changes in cytokines and/or growth factors, alterations in hepatic blood supply and enhanced cellular host response promoting local tumor growth after PVE. Growth factors such as IL-6, TNF-α and hepatocyte growth factor (HGF) are upregulated and play an essential role during liver regeneration after partial liver resection.19 The same growth factors have been implicated in stimulating growth of colorectal carcinoma cells in vitro. With respect to alterations in hepatic blood supply, compensatory, increased arterial perfusion, known as the hepatic arterial buffer response, occurs after reduction of portal blood flow.19 Because liver tumors are mainly vascularized by the hepatic artery, the hepatic arterial buffer response therefore potentially stimulates tumor growth in the embolized liver lobes. Other factors such as heat shock protein-70 (hsp70), heme oxygenase-1 (hmx-1) and plasminogen activator inhibitors (PAI-1) have been shown to facilitate growth and angiogenesis in solid tumors.20 The time to clinical outgrowth of micrometastases in the future remnant liver after PVE can also be viewed as a diagnostic window. Small metastases, not detectable on CT scan before embolization, may become visible after PVE, rendering the patient unresectable or requiring reconsideration of management (Figure 3). It may be assumed that if PVE had not been performed preoperatively, these metastases would have become apparent in the first few weeks after resection, as a result of the same growth-inducing factors associated with post-hepatectomy regeneration.

Although difficult to accurately estimate, the impact of tumor progression after PVE underscores the importance of minimizing the waiting time between PVE and resection, and of devising therapeutic strategies using chemotherapy to control tumor growth after PVE. Sequential hepatic transcatheter arterial chemo-embolization (TACE) after PVE as well as post-PVE chemotherapy have been used to prevent tumor progression. Several recent studies suggest that continuation of chemotherapy after PVE has no negative influence on the hypertrophy response or on the outcome after resection.13,21,22 The combination of TACE and PVE has the advantage of reducing post-PVE reperfusion through arterial-portal shunts, hence enhancing the regenerative response in the non-embolized lobes. An additional effect is the curbing of tumor progression by selectively cutting off arterial blood supply. Especially highly arterialized tumors such as hepatocellular carcinomas are likely to grow because of the compensatory increase of arterial blood flow after PVE. Sequential application of
TACE and PVE limits the risk of ischemia and infarction of the liver parenchyma, as has been shown in experimental as well as clinical studies. The Beaujon group in Paris reported a study in which PVE combined with TACE (mean time interval 3.6 weeks) was compared with PVE alone in patients with hepatocellular carcinoma and cirrhosis. The mean increase in FRL volume and the rate of hypertrophy were significantly higher in the group in which PVE was combined with TACE. Using this combination, complete tumor necrosis was achieved in 80% of the patients compared to 5% in the PVE group, also with a higher 5-year disease-free survival rate in the former group.

What is the optimal timing of resection after PVE?

Tumor progression after PVE creates a dilemma in terms of optimal waiting time until resection. The risk of tumor growth obviously demands an as short as possible waiting time. The time interval is mainly determined by the time required to attain the target FRL volume. According to a meta-analysis, the length of time after PVE to operation was 2-60 days. Usually, a period of 3-4 weeks is considered sufficient based on CT volumetry. Asian surgeons tended to wait shorter until operation, whereas in Europe and the US, waiting times were longer. Of note, however, is that the functional increase of remnant liver likely exceeds the volume increase of remnant liver mass. The recommended waiting time may therefore be shorter than based on volumetric...
studies. The regeneration rate of the nonembolized liver segments typically shows an increase during the first 3 weeks after PVE, followed by a plateau phase with only slight additional increase of FRL volume (Figure 4). Patients showing slow growth of the FRL and those with a persistently small FRL volume after 3 weeks are unlikely to exhibit rapid regeneration beyond this time point; further extension of the waiting time, therefore, seems futile. In a study performed by Ribero et al. from M.D. Anderson Cancer Center in Houston, a low degree of hypertrophy as a measure of liver growth was identified as a predictor of poor clinical outcome after resection. In this regard, PVE may be used as a ‘stress test’ to assess the regenerative potential of the FRL in the most crucial period, i.e. the first 3 weeks after PVE. In our center, CT volumetry and 99mTc-Mebrofenin hepatobiliary scintigraphy as a test of liver functional reserve are performed on the 21st day after PVE. If the increase in volume and function is insufficient, CT and 99mTc-Mebrofenin hepatobiliary scintigraphy is repeated 14 days later. At that time, the patient is operated or resection is declined when FRL volume and/or function are considered insufficient.

**Figure 4.** Graph showing the regeneration rate of the non-embolized liver segments after PVE. Volume increase of future remnant liver is greatest during the first 3 weeks after PVE, after which a plateau phase follows with only slight additional increase of volume. FRL volume at baseline was 28.2%, and increased to 36.5 and 40% at 21 and 48 days after PVE.

**Does PVE render the posthepatectomy hypertrophy response less effective?**

The mechanisms underlying hypertrophy of the nonembolized liver segments after PVE are probably similar to the mechanisms triggering posthepatectomy hypertrophy of the remnant liver segments following liver resection. The question arises whether the hypertrophy response after liver resection and prior PVE is as efficient as after liver resection only. Considering that liver regeneration is an energy-consuming process, one might speculate that the resources responsible for posthepatectomy regeneration are to some extent exhausted after previous PVE. To examine this, we
performed CT volumetric studies in patients who underwent PVE prior to (extended) right hemihepatectomy, using patients as controls who underwent the same type of resection without prior PVE. CT volumetry 3 months after hemihepatectomy showed no significant difference in the increase of remnant liver volume after resection in patients who underwent (extended) right hemihepatectomy with or without prior PVE (Figure 5). Hence, the regenerative capacity of the liver is not hampered after PVE and subsequent major liver resection, showing the same hypertrophy response as after liver resection alone.

![Graph showing increase of remnant liver volume at three months after (extended) right hemihepatectomy in 10 patients who had undergone PVE 3–4 weeks prior to resection (thin lines). Fat line represents the mean increase of remnant liver volume in 13 patients who had undergone (extended) right hemihepatectomy without preoperative PVE (control group). Posthepatectomy regeneration was not hampered after PVE as remnant liver volumes attained approximately 80% of initial total liver volume in both groups.](image)

**Discussion**

PVE is increasingly used to preoperatively enlarge the FRL in patients with increased risk of postoperative liver failure. Although probably not in the same proportion, increased FRL volume translates into increased functional reserve of the liver remnant after resection. Preoperative diversion of the portal flow creates another advantage in terms of venous outflow of the liver remnant. Division of the portal branches of the part of the liver to be resected results in an immediate increase in flow through
the portal bed of the liver remnant. With extensive resection (70%), the volume of portal blood directed through the liver remnant is tripled, which requires immediate adaption of the portal venous bed to accommodate the larger volume of portal blood. This ‘small for size’ situation may lead to a relative venous outflow block and liver congestion which impede function and the capacity of the remnant liver to regenerate. Preoperative PVE allows for the FRL to preadapt to the increase in portal flow reducing the risk of the hyperperfusion syndrome and hepatic venous congestion directly after resection.

Inasmuch as we understand the mechanisms of regeneration after liver resection, we understand the biologic process of regeneration of the nonembolized lobe after PVE. It is not known which factor(s) set(s) off the cascade of cytokines and growth factors responsible for regeneration after PVE. The dramatic increase in portal blood flow through the remnant liver after partial liver resection is considered an important trigger for liver regeneration. Experimental studies have demonstrated that decreased portal flow in the remnant liver is associated with an impaired or delayed regenerative response. PVE results in a similar increase in portal perfusion to the FRL, which in turn is potentially responsible for post-PVE regeneration. However, one might speculate that posthepatectomy regeneration after prior PVE is less effective than posthepatectomy regeneration without prior PVE, because portal perfusion of the liver remnant after PVE and subsequent hemihepatectomy is largely unchanged. As dealt with above, the hypertrophy response after liver resection, however, is as efficient as without preceding PVE, suggesting other mechanisms to induce regeneration than only hemodynamic factors.

An interesting concept has been introduced by Lainas et al. concerning reversible PVE. In a model of PVE in monkeys, biodegradable gel foam was used resulting in an initial, complete occlusion of the hemihepatic portal venous system, followed by revascularization of this system within 13 days, as the embolization material was gradually absorbed. The authors noted an efficient hypertrophy response of the nonembolized lobe in spite of the nonpermanent occlusion of the contralateral portal venous system, suggesting that a short period of portal occlusion suffices to initiate the process of regeneration in the nonembolized lobe. This approach obviously introduces some important advantages, as the embolized lobe, when not resected for whatever reason, is not left with decreased function. Secondly, inadvertent backflow of the embolization material to the nonembolized lobe will cause less harm and not preclude regeneration of the FRL. The concept of reversible PVE underscores the need for clinically relevant animal models to study PVE in conjunction with the mechanisms of PVE and new embolization materials.
Conclusion

PVE is a useful preoperative intervention to increase volume and function of the FRL when planning extensive liver resection, especially in patients with compromised liver parenchyma or when associated with additional, major gastrointestinal procedures. The hypertrophy response after PVE has predictive value in regard with posthepatectomy outcome. Procedure-related complications after PVE (hematoma, hemobilia, sepsis, backflow of embolization material and thrombosis of portal vein branch(es) of the nonembolized lobe) should not be underestimated, and avoidance of adverse events requires expertise of interventional radiologists and liver surgeons. Because the overall liver volume and function after PVE remains unchanged, the persistence of the embolized, atrophic lobe usually does not generate an additional risk. Embolization of the portal branches to segment 4 in addition to embolization of the right portal trunk carries increased risk and is advised only in selected cases. It is as yet undetermined whether embolization of the portal venous system is more effective in inducing hypertrophy of the FRL than ligation of the portal vein. Accelerated tumor growth after preoperative PVE is a major concern and requires appropriate timing until resection in conjunction with effective chemotherapy around the procedure. Otherwise, the benefit of upsizing the liver may be counterbalanced by upsizing tumor load. A waiting time of 3 weeks is advised since beyond that time, additional increase of FRL volume is limited. Posthepatectomy regeneration is not hampered by preoperative PVE. The mechanisms of the hypertrophy response need to be elucidated in order to render PVE more effective, in conjunction with new embolization materials and new strategies such as reversible PVE.
References