Portal Vein Embolization

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T. Hashimoto and M. Makuuchi

Abstract

Preoperative portal vein embolization (PVE) is performed to increase the safety of major hepatic resection which reduces the volume of the liver and raises the portal pressure immediately after operation. PVE induces atrophy of the embolized portion of the liver to be resected, with compensatory hypertrophy of the contralateral portion of the future preserved liver remnant. Today, PVE is widely accepted as a standard preoperative procedure for patients with hilar cholangiocarcinoma.

14.1 Introduction

In patients with hilar cholangiocarcinoma, radical surgery out performs any other therapeutic modalities in survival rate and quality of life [1]. To improve survival for hilar cholangiocarcinoma, curative resection after good preoperative management is an important approach [2]. Minimal resection of the involved segments, such as en-bloc caudate lobectomy, paramedian sectorectomy with caudate lobectomy, and central hepatectomy have been selected on the basis of the extent of cancer invasion to minimize the risk of postoperative hepatic failure [3, 4]. However, in many patients with hilar cholangiocarcinoma, limited hepatectomy is insufficient, and extended hepatectomy is required to obtain a negative surgical margin for cancer. Extended hemihepatectomy has recently been recognized as the standard curative treatment for hilar bile duct cancer and has an acceptable mortality [5–9]. Major hepatectomy, concomitant with pancreaticoduodenectomy has been applied to selected patients with advanced tumors [7, 8, 10–12]. However, these extensive radical procedures are not always safe, because there are risks of postoperative liver failure, especially after extended right hepatectomy. The greater the volume of liver resected, the greater the risk for patients to develop postoperative hepatic failure due to insufficient remnant liver volume.

In 1982, to overcome this problem, Makkuchi et al. carried out the first preoperative portal vein embolization (PVE) on a patient with hilar bile duct carcinoma scheduled to undergo a major hepatic resection [13, 14]. This approach was based on the concept of hepatic "atrophy-hypertrophy complex". The concept dates back to 1920 when Rous and Larimore ligated a major branch of the portal vein in a rabbit, and successfully acquired atrophy of the ipsilateral hepatic lobe and hypertrophy of the contralateral lobe [15]. Later, in 1975, in an effort to suppress tumor growth, Honjo et al. ligated the ipsilateral portal venous branch in patients with hepatocellular carcinoma (HCC) [16]. Although the approach did not succeed in preventing tumor growth, it did produce marked atrophy of the occluded part of the liver. Likewise, patients with hilar bile duct carcinoma involving a branch of the portal vein experienced an uneventful postoperative clinical course after extensive hepatectomy as the tumor caused partial liver atrophy and corresponding hypertrophy of the contralateral portion of the liver [17].

Major hepatectomy induces reduction in liver volume and raises portal pressure immediately after operation. If PVE is performed preoperatively, the portal pressure would already have been raised at the time of PVE and a slight increase in size can be observed in the remnant liver. PVE has dramatically increased the safety of hepatic resection, and consequently, the indication for PVE has now been extended to other diseases; such as HCC, intrahepatic cholangiocarcinoma, and metastatic liver tumors [18].

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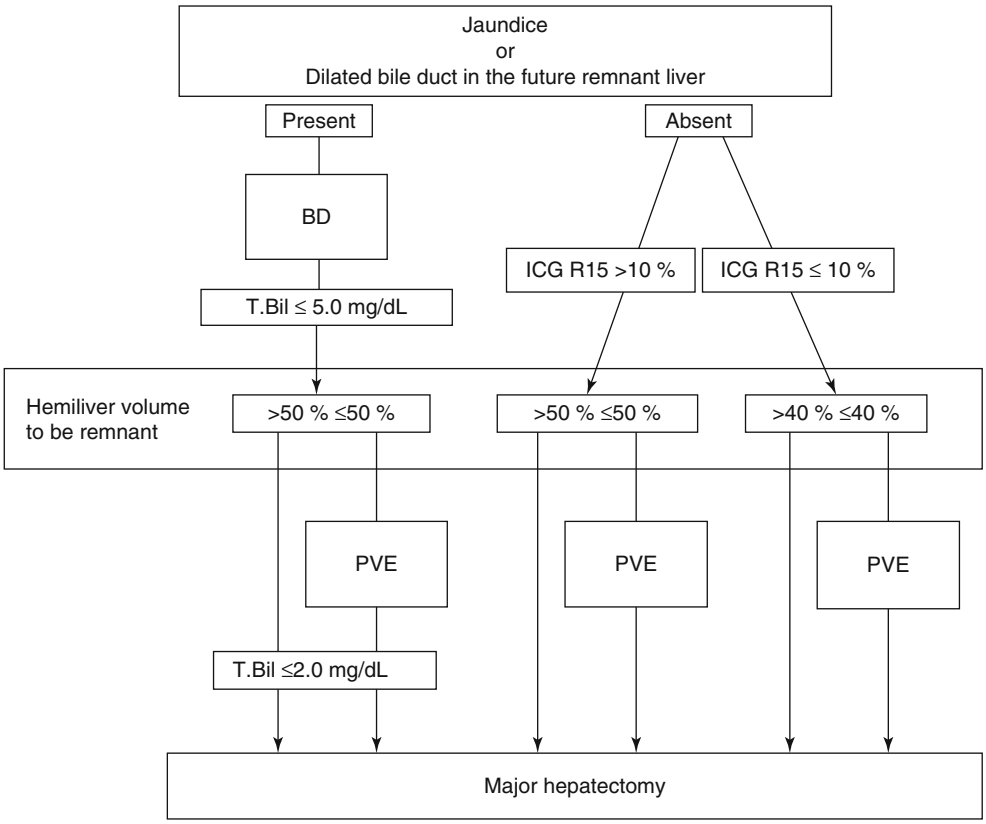

Fig. 14.1 Flowchart for preoperative treatments. When jaundice or dilated bile ducts in the FRL is observed, biliary drainage (*BD*) is performed. Surgical interventions are scheduled after sufficient recovery of the hepatic function. Portal vein embolization (*PVE*) is carried out to avoid postoperative liver failure, which is dependent on the liver function and the liver volume to be resected

14.2 Indications for PVE

Seyama et al. described a safe strategy for hilar bile duct cancer which included biliary drainage and PVE [8]. A flow chart for preoperative treatment is shown in Fig. 14.1. If the patient showed evidence of jaundice, or dilated bile ducts in the future remnant liver (FRL) was detected, biliary drainage was performed, but in principle only to the FRL. Whether PVE was indicated depended on the liver function and the volume of the FRL as calculated by CT volumetry. In patients with normal liver function, i.e. patients with ICG R15 value under 10 %, PVE was indicated when the remnant hemiliver volume was less than 40 %. In patients with jaundice or with ICG R15 value over 10 %, PVE was indicated if the remnant hemiliver volume was less than 50 % [19]. Since the standard operative procedure for hilar bile duct cancer is an extended hemihepatectomy including the whole segment 1, the remaining hemiliver volume should have a margin above the safety zone. After PVE, hepatectomy was performed after re-evaluation of the liver volume, and only when the patient had fulfilled the criteria. Figure 14.2 shows the intraoperative findings after biliary drainage of the FRL followed by PVE of the right portal vein. The right liver was markedly atrophic, and a biliary drainage tube was inserted into the bile duct in segment 3, which drained only the future remnant left liver. Extended right hemihepatectomy was carried out for this patient.

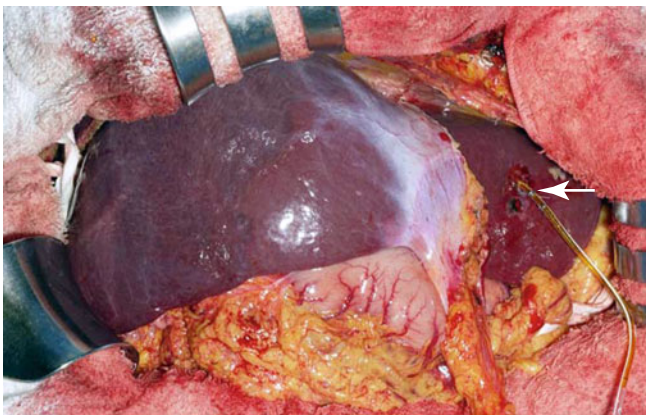

Fig. 14.2 Intraoperative view at laparotomy after biliary drainage and PVE. A percutaneous transhepatic biliary drainage tube (*white arrow*) is inserted into the bile duct of segment 3. The right liver is markedly atrophic, and there is a clear line of demarcation between the right and left liver

Sometimes we experience patients to whom hemihepatic biliary drainage has been carried out but the serum total bilirubin decreases slowly and does not reach the target level of under 5.0 mg/dl, which is the indication criteria for PVE. For such patients, we aggressively perform PVE to the undrained hemiliver before the serum total bilirubin can finally reaches the target level of within the criteria. After PVE, the rate of decrease of the serum total bilirubin rapidly improves. One

point never to be forgotten is that during prolonged biliary drainage, cholangiography must not be carried out because it induces cholangitis and increases the risk of postoperative infectious complications. Do not perform cholangiography especially when the right and left bile ducts are not communicating. If a need for cholangiography arises during the prolonged waiting period from the time of the drainage to the operation because of unsatisfactory serum bilirubin or to show regeneration of the FRL, cholangiography should be carried out in the afternoon on the day prior to the radical operation.

14.3 Types of PVE

Basically, the portal branches in the liver to be resected are embolized according to the criteria previously described. In most cases of extended right hemihepatectomy, portal vein embolization of the right hemiliver (right PVE) is required. When the tumor is located predominantly in the left hepatic duct, and left trisectorectomy is scheduled, embolization of the left portal vein and the portal vein of the right paramedian sector is performed. When the FRL volume is smaller than expected for an extended left hemihepatectomy, the left portal vein is embolized. In some cases in which the serum total bilirubin is still high even after adequate biliary drainage, portal vein embolization of the liver to be resected is carried out in order to decrease the serum bilirubin and improve the liver function.

It is still controversial whether the portal branches to segment 4 should be embolized when an extended right hemihepatectomy or a right hemihepatectomy with segment 4 resection is scheduled. Because the portal branches to segments 2, 3, and 4 usually originate from the umbilical portion, insufficient hypertrophy of segments 2 and 3, and unwanted hypertrophy of segment 4 is expected after right portal branch embolization alone. The right plus segment 4 embolizations through an ipsilateral approach have been reported [20, 21]. Right liver plus segment 4 PVE has been proven to be more effective than the standard right PVE as preparation for right hemihepatectomy plus segment 4 resection, and it also has the potential in increasing the safety of high-risk surgery for patients with hilar cholangiocarcinoma. Madoff et al. [22] also reported on the effectiveness of segment 4 embolization. On the other hand, Capussotti et al. [23] reported that extension of embolization to segment 4 portal branches should not be routinely carried out because a similar volume increase of segments 2–3 could simply be achieved by right PVE. In general, the portal branching pattern of segment 4 is not simple. Several small branches run to the segment 4 from the umbilical portion, in addition to the major branches which run to the superior and inferior parts of the segment 4. The liver volume supplied by these small branches cannot be neglected.

The standard procedure for hilar cholangiocarcinoma is extended right hemihepatectomy. The inferior part of segment 4 is resected with the right hemiliver and the caudate lobe, in order to resect the left hepatic duct as much as possible. Before this procedure, right PVE had been performed for anatomical reasons as described before. The postoperative courses of our patients were uneventful.

14.4 Technique of PVE

There are three standard approaches which may be chosen for PVE: the intraoperative transileocolic venous approach; the transhepatic contralateral approach (i.e., portal access via the FRL); and the transhepatic ipsilateral approach (i.e., portal access via the liver to be resected). In general, an approach is chosen based on the type of hepatic resection planned, location of tumor, extent of embolization, and availability of the surgical and radiological facilities. For most patients with hilar cholangiocarcinoma, the first choice is the transhepatic ipsilateral approach. This procedure is ideal because the FRL would not be injured by the puncture. However, when the bile ducts in the future resected liver are dilated and are not drained, this procedure may carry the risk of bile leakage from the needle tract. Intraoperative transileocolic venous approach is generally the second choice.

In every step of the procedures, portal vein anomalies should be investigated by ultrasound (US) or computed tomography (CT) prior to PVE (Fig. 14.3), and by direct portography at the commencement of embolization (Fig. 14.4), paying particular attention to whether or not second-order branches originate close to, or independently of, the main portal trunk. Right anterolateral fluoroscopy is recommended during embolization of the branches to segments 6 and 7. Rare but indismissible technical failures are usually associated with difficulty in catheterization due to severe angulations between the portal branches and the migration of embolization materials. To overcome the narrow angulations, several preshaped catheters should be prepared. Use of a balloon-tipped catheter is advocated to avoid the complication of migration of embolization materials.

14.4.1 Transileocolic Venous Approach

Transileocolic venous approach is performed during laparotomy under general anesthesia by direct cannulation of a catheter into the ileocolic vein inserted and advanced under the guidance of a wire, which is then replaced by a balloon catheter at the portal vein for subsequent embolization under fluoroscopic guidance [13, 14]. This approach is often performed when an interventional radiology suite is not available, percutaneous approach is not feasible, or when an

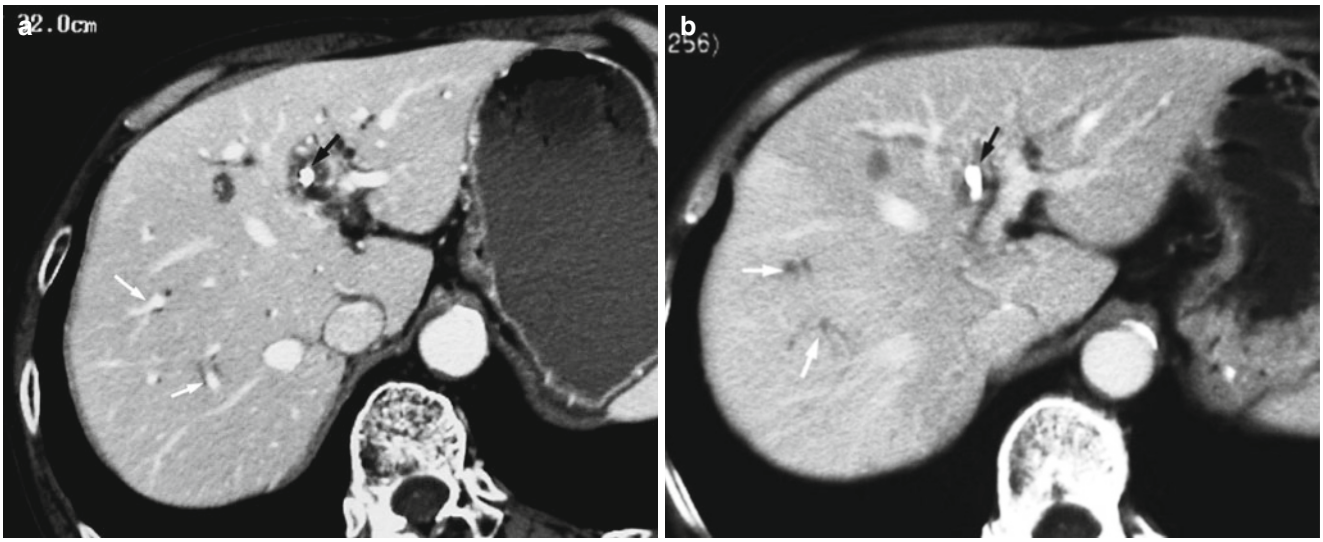

Fig. 14.3 CT scan images of a 70-year-old woman with hilar bile duct carcinoma (**a**) before and (**b**) 2 weeks after PVE carried out to the right liver with gelatin sponge particles and thrombin. Coil was not used for this patient. The *black arrow* indicates a percutaneous transhepatic biliary drainage catheter. The *white arrows* indicate portal tributaries to segment 8. Note the cessation of portal flow and the attenuation difference by HABR in the right liver after PVE

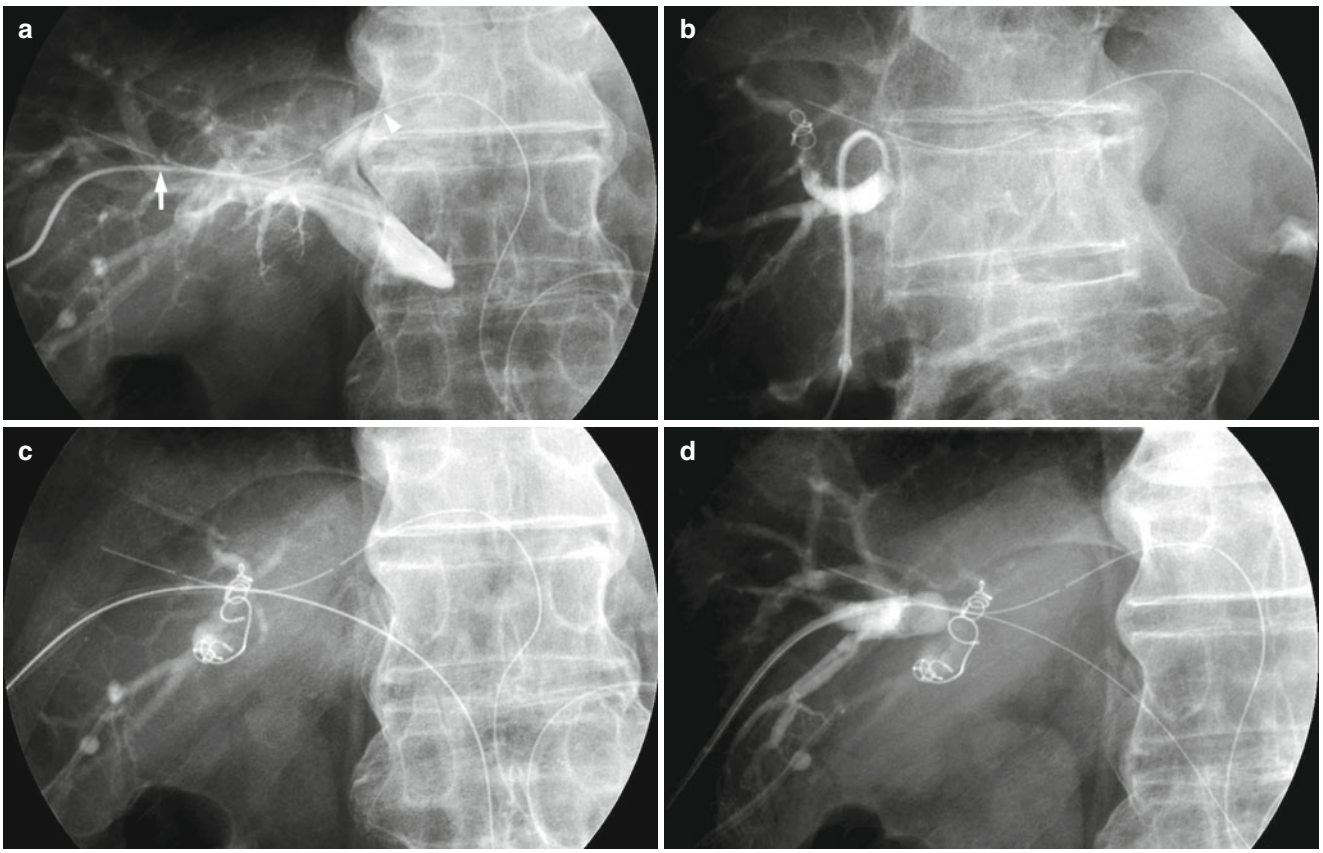

Fig. 14.4 Transhepatic ipsilateral right PVE with gelatin sponge particles, thrombin, and coils carried out on a 72-year-old man with hilar bile duct carcinoma. (**a**) Anteroposterior flush portogram obtained before right PVE with the use of a 6-F vascular sheath in segment 5 portal branch, and a 5-F flush catheter in the main portal vein (*arrow*). The *arrowhead* indicates the percutaneous transhepatic biliary drainage catheter (anteroposterior fluoroscopy view). (**b**) Embolization was commenced from the portal branch to segment 7 with a reverse-curve catheter with distal end-hole under right anterolateral fluoroscopy (anterolateral fluoroscopy view). (**c**) Completion of the embolization carried out to portal branches to segments 6 and 7. Tip of the catheter was placed in the main portal vein (anteroposterior fluoroscopy view). (**d**) Embolization of portal branches to segments 5 and 8 with proximal side-hole type catheter (anterolateral fluoroscopy view). (**e**) Completion of PVE. Coils were placed at the root of the portal branches to segments 5, 6, 7 and 8 (anterolateral fluoroscopy view)

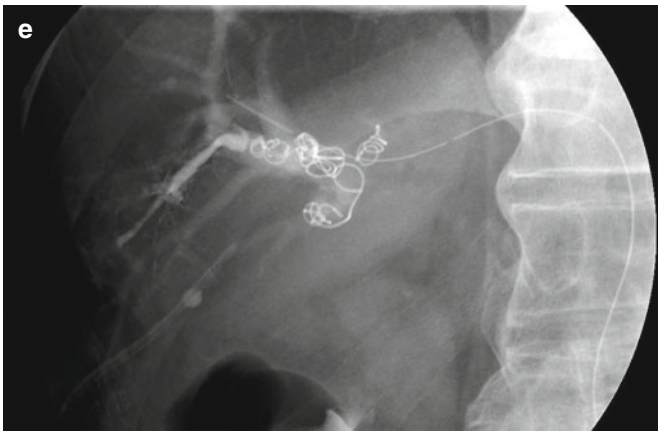

Fig. 14.4 (continued)

additional treatment which may be carried out during the procedure has become necessary [24]. One of the advantages of this approach is that it is possible to evaluate the extent of the tumor at the time of PVE including peritoneal dissemination and hilar lymph node metastases [25]. Catheterization of all portal tributaries is simple even in cases with anatomical variations. However, open laparotomy under general anesthesia is required and this technique is not suitable for patients with a history of prior lower abdominal surgery. Intestinal ileus has been reported to occur [25].

14.4.2 Transhepatic Approach

Transhepatic procedure may be performed under local anesthesia, and intravenous sedatives may or may not be administered. US examination of the liver is carried out to determine the most favorable access route into the portal venous system. Under sterile condition, access into the portal venous system is gained under ultrasonic and fluoroscopic guidance. The contralateral approach (access through the FRL) is technically easier than the ipsilateral approach (access through the portion of the liver to be resected), especially in the presence of anatomical variations [26].

The transhepatic contralateral approach was the most commonly used technique in the early periods [27]. For embolization of the right portal branches, a branch of the left portal system is chosen for access, and a balloon occlusion catheter is advanced through an introducer into the branches of the right portal tree. The major advantage of this approach is the operative simplicity. Catheterization of the desired right PV branches is easily accomplished from the left side. The drawback of this method on the other hand, is that the portal vein in the FRL is punctured. Iatrogenic lesions of the FRL lobe, including hematoma, portal vein wall dissection, and portal vein thrombosis, have been reported in a multicenter review [28].

Transhepatic ipsilateral approach was first described by Nagino et al. [29]. The peripheral portal vein branch in the liver to be resected is secured, and a sheath is inserted through. One apparent advantage of the ipsilateral approach is that the FRL is not injured. Embolization materials or coils are placed along the puncture line upon completion of the procedure to prevent post-PVE hemorrhage. However, this approach is technically more demanding than the contralateral approach. A balloon occlusion catheter with a side lumen opening just proximal to the balloon is occasionally required to avoid unintended embolization of the FRL. When the angle of the right portal branches is severe, the use of reverse-curved catheters becomes necessary. Furthermore, it is usually difficult to perform post-PVE portography or portal pressure measurement to confirm the efficacy of embolization with this procedure.

14.5 Embolization Materials

There is no clear general consensus on the choice of embolization material for PVE. Biomaterials including gelatin sponge particles or powder with thrombin [25] and fibrin glue (combination of fibrinogen and thrombin) [29, 30], synthetic glue (n-butyl-2-cyanoacrylate) [26], synthetic embolization particles (polyvinyl alcohol) [31, 32], coils, iodized oil, and absolute ethanol [33] are used. These materials have yielded different rates or degrees of hypertrophy of the unembolized segments, and the choice of embolization material usually depends on each surgeon's or institute's preference [34]. While absorbability of biomaterials allow unwanted recanalization, the same characteristic also keeps the damage caused by unintended migration of embolization materials during the procedure into the portal branches of the FRL to a minimum or is completely absent [25]. N-butyl-2-cyanoacrylate immediately polymerizes upon contact with blood (water) and has a permanent embolizing effect. However, massive peribiliary fibrosis and portal vein casting [26] it induces may lead to difficulty in dissecting the hilar region or in evaluating tumor invasion [33]. Polyvinyl alcohol particles have a smaller diameter (150–100 μm) than gelatin sponge (500–100 μm). This material is selected for its safety in use, minimal periportal reaction, and sustainable embolization effect when used in combination with coils [32]. Coils and iodized oil are usually used in combination with these materials. Iodized oil in particular is used because of its long-lasting "portal cast" effect which may be viewed on follow up plain X-ray film and CT scans. PVE with absolute ethanol had been proposed because of its strong coagulation effect [33], and hypertrophy appeared to be more significant than with other materials. However, PVE with absolute ethanol has been associated with a marked increase in serum aspartate aminotransferase

(AST) and alanine aminotransferase (ALT) levels, which in turn, may lead to necrosis of the embolized region [33]. We have to be careful when selecting absolute ethanol, especially for patients undergoing hemiliver biliary drainage. Damage inflicted to liver parenchyma by ethanol injection would be more severe on the hemiliver without biliary drainage than on the hemiliver with adequate biliary drainage. If the whole right hemiliver is necrotized by using absolute ethanol, critical hepatic failure would occur and postoperative course after PVE would be miserable. The basic concept of PVE is that it induces increment of portal pressure, and progression of apotosis of the embolized liver, which in turn gradually produces atrophic and hypertrophic changes of the liver. However, if increment of portal pressure and necrosis occur at the same time from using ethanol, the clinical course is the same as that of extended hepatectomy without preoperative PVE.

We routinely use gelatin sponge powder with thrombin. This material is less harmful than others and the effect is enough for sequential hepatic resection. When recanalization of the embolized portal branches is detected during the follow up period, the recanalized portal branches are selectively punctured to inject absolute ethanol. The use of absolute ethanol for embolization in a small part of the liver is considered acceptable.

14.6 Portal Pressure After PVE

Total portal venous flow (ml/min) is unaffected by PVE because the liver does not have an intrinsic ability to modulate portal flow, and that it is a function of extrahepatic and systemic factors. In a PVE study on human, this was confirmed using Doppler US [35]. Because the same volume of portal flow prior to PVE enters the non-embolized lobe after PVE, portal pressure in the non-embolized liver is elevated immediately after PVE by 4.9 ± 2.7 cm H_2O [36]. A similar increase was observed in cirrhotic patients with a higher baseline portal pressure [37]. The elevation of portal pressure is transient, with pressure gradually returning to the baseline value in 2–3 weeks, as indicated by the portal flow velocity (cm/s) changes measured by Doppler ultrasound [38].

14.7 Clinical Course After PVE

Signs and symptoms of postembolization syndrome due to PVE itself, such as pain, fever, nausea, and vomiting, are milder and less than transcatheter arterial embolization (TAE). Most patients experience a mild fever following PVE, which subsides within 2–3 days. Changes in liver function as reflected by an increased total bilirubin and prolonged prothrombin time are mild and transient, returning to their baseline values 2–3 days after PVE. Serum levels of AST and ALT are stable in about 50 % of patients. They are mildly elevated on day 1, then returning to the baseline values in 4–7 days after PVE. These findings suggest that inflammatory and/or necrotic reactions after PVE are minimal, if at all, present [25]. The exceptions are when absolute ethanol is used [33] for embolization. When absolute ethanol is used for PVE, it is followed by a marked rise in serum AST and ALT, though both tend to return to their baseline values by 2 weeks before the scheduled hepatectomy.

In western countries, an evaluation of liver volume is carried out 4–6 weeks after PVE. The waiting period between PVE and operation is reported to be shorter in Japan (2–3 weeks), but this has been proven to be quite adequate in performing hepatic resection safely.

14.8 Volumetric Changes After PVE

In order to determine whether PVE is necessary before hepatic resection, and to assess the degree of FRL hypertrophy, the ratio of "FRL volume/Total liver volume-Tumor volume" (the FRLV/TLV ratio) is widely used as a parameter. CT scan with contrast material is the most commonly used method for calculating noncancerous total liver volume and FRL volume. Examination using CT scan should be performed before and after PVE. Multi-slice helical CT scan or multidetector CT scan with contrast material allows accurate volumetric measurement by subtracting the small tumor volumes and vasculo-biliary structures at the Couinaud's segment level.

PVE leads to an increase in the segmental volume of a non-embolized liver, and a decrease in an embolized liver, homogeneously maintaining a constant total liver volume. The regeneration rate of the non-cirrhotic liver has been reported to be 12 cm^3/day 2 weeks after PVE [30, 39], then falling to 11 cm^3/day at 4 weeks [30], and 6 cm^3/day at 32 days [26]. In general, a 30 % increase in the non-embolized liver volume being an absolute value, and a 10 % increase as expressed by the FRLV/TLV ratio, are attained 2 weeks after right liver PVE.

Various factors have been reported to affect the regeneration rate after PVE. The greater the FRL volume before PVE, the smaller the volume increase after PVE [25, 40, 41]. The magnitude of hypertrophy differs with the materials used for PVE. Hypertrophy appears to be moderate when biological materials such as gelfoam and fibrin glue are used, most probably because of their progressive recanalization effect. Absolute alcohol has been reported to achieve the highest degree of regeneration. However, it is accompanied by marked increases in serum AST and ALT, and an increased risk of liver necrosis. Thus, absolute alcohol is not a good choice as an embolic material for PVE. Diabetes, obstructive jaundice, and active hepatitis have been reported to hamper the regeneration process [25, 30]. In cirrhotic patients, the regeneration rate is smaller than in non-cirrhotic patients. Their reported regeneration rate is 9 cm^3/day at 2 weeks [26, 39].

14.9 Histological Changes After PVE

In a human study, liver tissues obtained 3 weeks after PVE have shown almost normal microscopic structures in both the embolized and the non-embolized lobes. However, in the embolized lobe, dilatation of sinusoids with decreased hepatocyte density and hepatocyte apoptosis, especially in the pericentral area, were observed [42]. There were no signs of necrosis or inflammation in the embolized lobe, except for the liver tissues of the embolized lobe which had undergone PVE using absolute ethanol [33], with clear evidence of necrosis. When cyanoacrylate is used for PVE, peribiliary fibrosis is induced [26]. Microscopic findings of the non-embolized liver on the other hand, have shown hepatocyte replication as evidenced by increased mitotic figures and other parameters of cell proliferation such as the levels of proliferative cell nuclear antigen and Ki-67 [42, 43]. Hepatocytes in this liver were histologically characterized by basophilic cytoplasm, abundant binuclear cells, and they were small. The observation provides indirect evidence of hepatocyte proliferation [42].

14.10 Functional Changes After PVE

Considering proliferating isolated hepatocytes lose their differentiated hepatocyte-specific functions, cellular hyperplasia and the resulting partial hypertrophy do not necessarily signify functional gain in the corresponding part of the liver. Most reports investigating liver function after PVE had assessed the whole liver function, including both the embolized and the non-embolized lobe. The overall functional hepatocyte number, as estimated by the clearance of antipyrine, a prototype low-extractable drug, has shown similar values before and 2 weeks after PVE [44]. When ATP concentrations and hepatic energy reserves per *g* of liver tissue were assessed in the non-embolized lobe 3 weeks after PVE, the values were similar to those of the control tissue [45]. Likewise, the non-embolized lobe uptake of technetium-99 m-galactosyl human serum albumin (^{99m}Tc-GSA), a ligand bound to asialoglycoprotein receptors on the hepatocyte cell membrane, showed a rapid increase 1–2 weeks after PVE [46, 47]. These findings demonstrate that the volume increase in the non-embolized liver is accompanied by a parallel increment of liver function in the corresponding part.

Conclusion

PVE is indispensable for extensive liver resection for hilar cholangiocarcinoma. Although randomized controlled study has not been conducted, its effectiveness is widely accepted. However, one should not forget that PVE is only a "preoperative procedure" whose aim is to assist in the safety of liver resection. Complications arising from PVE therefore are preposterous. PVE should be performed promptly and without any complications.

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