

Portal vein embolization with different embolic agents for right hepatectomy

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Background/aims: We aimed to retrospectively evaluate our experience in portal vein embolization that induces hypertrophy of the future liver remnant before right hepatectomy and to determine the differences in outcome with respect to the embolic agents used. **Methods:** Twenty right portal vein embolization procedures performed in our institution between 2004 and 2009 were reviewed in this study. The average patient age was 59 years (range: 45-72 years). Embolization was performed through a right portal vein percutaneous access with use of the combination of several agents. Computed tomography volumetry was performed before and 4-6 weeks after the procedure to measure total liver volume and future liver remnant. **Results:** There was no major complication related to the embolization procedures. After embolization, future liver remnant / total liver volume ratio increased to 12.7%, which was statistically significant. No significant difference was noted in hypertrophic outcomes between alcohol and the other embolic agents. Although five patients had sufficient future liver remnant, they did not undergo subsequent hepatectomy for a variety of reasons. **Conclusions:** According to our results, the mean increase in the size of the future liver remnant was greater than reported in previous studies of portal vein embolization. Despite the limited patient number of our study, we believe that portal vein embolization is helpful especially in gray-zone patients who may be a good candidate for surgical resection and thus possible cure. However, randomized, controlled studies with hypertrophy-inducing agents are needed.

Key words: Portal vein embolization, liver, computed tomography

Sağ hepatektomi öncesinde değişik ajanlarla yapılan portal ven embolizasyonu

Amaç: Bu çalışmada sağ hepatektomi öncesinde kalan karaciğer hacmini artırmak için yapılan portal ven embolizasyonu ile ilgili deneyimlerimizi retrospektif olarak sunduk ve farklı embolizan ajanların etkinliğini araştırdık. **Yöntem ve Gereç:** Bu çalışmada 2004 ve 2009 yılları arasında merkezimizde 20 olguya portal ven embolizasyonu uygulandı. Hastaların ortalama yaşı 59'du (45-72 yaşları arasında). Embolizasyon değişik ajanların kombinasyonu kullanılarak sağ portal vene perkütan girişimle yapıldı. İşlemden önce ve 4-6 hafta sonra total karaciğer hacmini ve karaciğer hacmini hesaplamak için bilgisayarlı tomografi volümetri yapıldı. **Bulgular:** İşleme ilgili major komplikasyon görülmedi. Embolizasyon sonrası karaciğer hacmi / total karaciğer hacmi oranı %12.7'lere çıktı ve bu istatistiksel olarak anlamlıydı. Alkol ve diğer embolizan ajanlar arasındaki sonuçlarda istatistiksel olarak anlamlı farklılık yoktu. 5 hastada belirgin karaciğer hacmi olmasına rağmen çeşitli nedenlerden dolayı hepatektomiye gidilmedi. **Sonuç:** Bizim olgularımızda karaciğer hacmi ölçümlerindeki artış daha önceki bildirilen portal ven embolizasyonu çalışmalarından daha fazlaydı. Çalışmamızda, hasta sayısı az olmasına rağmen portal ven embolizasyonunun gri zon hastalar için cerrahiye iyi bir aday oluşturması ve böylece olası kür sağlaması açısından yardımcı olduğuna inanıyoruz. Bununla birlikte embolizan ajanların karaciğer hacmi artırması ile ilgili kontrollü, randomize çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Portal ven embolizasyonu, karaciğer, bilgisayarlı tomografi

INTRODUCTION

Liver resection is the standard curative treatment of hepatobiliary malignancies. Extensive liver re-

section is often required for curative intent, which may lead to postoperative liver failure due to ina-

adequate liver remnant (1). Future liver remnant/total liver volume (FLR/TLV) ratio of at least 25% in patients with healthy liver and of 40% in patients with chronic liver disease is recommended. Preoperative portal vein embolization (PVE) is employed to increase the FLR in order to avoid this complication by the atrophy/hypertrophy mechanism. There are many reports describing the efficacy of PVE (2-4). The procedure is well tolerated with low complications. The resectability rate of previously inoperable tumor due to inadequate remnant liver volume is increased by PVE. The aim of this study was to describe our experience with PVE in hepatobiliary tumors at a single center.

MATERIALS AND METHODS

The clinical data of 20 patients (10 M, 10 F; age range: 45-72 years, mean: 59 years) who underwent PVE from January 2004 to December 2008 were reviewed. The preoperative diagnoses were liver metastases secondary to colon cancer (n=11), hepatocellular carcinoma (HCC) (n=6) and giant hemangioma (n=3). Preoperative PVE was indicated when estimated FLR volume was less than 20%. Written informed consent was obtained from the patients or their families before PVE. In the study group, there was no documented cirrhosis preoperatively in patients with HCC with grade A

chronic liver disease according to the Child Pugh classification.

Percutaneous puncture and subsequent PVE were performed under local anesthesia except for the cases with alcohol as the embolization agent, for whom general anesthesia was applied for pain management. The portal vein was accessed by puncture with a 19-gauge needle of the ipsilateral portal branch (access through the portion of the liver to be resected) under ultrasound (US) guidance. After placement of a 5F sheath in the portal vein, a 5F pigtail-catheter was inserted in the main portal trunk and digital subtraction portography was performed (Figures 1A, 2A). A reversed curve shaped (Simmons 1) catheter was then used for selective catheterization of the targeted segmental or subsegmental portal vein branches for delivery of the embolic material. Combination of several agents, including metallic coil, polyvinyl alcohol (PVA), absolute alcohol, and cyanoacrylate were used as embolizing materials. PVA (Contour, Cook, Bloomington, IL, USA) with metallic coils (Fibered platinum coils, 0.035 type and Vortex-18, Boston Scientific/Target Vascular, Cork, Ireland) in 7 patients, PVA-coils and absolute alcohol in 5 patients, n-butyl-cyanoacrylate (NBCA) in 3 patients, only absolute alcohol with no coils in 3 patients and coils-absolute alcohol in 2 patients were used. The endpoint of the procedure was complete

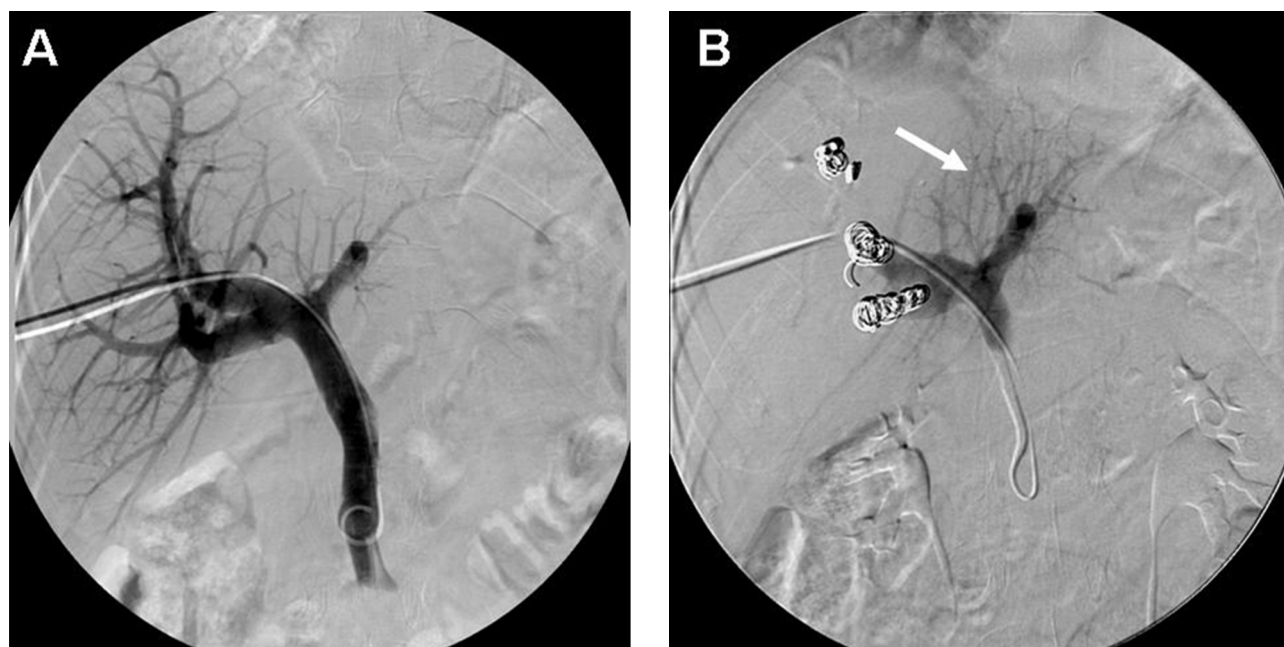


Figure 1. A, B: A 52-year-old man with metastatic colon carcinoma. **(A)** Anteroposterior main portal venogram obtained before PVE of the right portal venous branches. **(B)** Portal venogram shows a total occlusion of the portal venous branches in the right lobe. Left lobe portal venous branches became prominent (white arrow).

occlusion of the targeted portal veins, as assessed by direct portography (Figures 1B, 2B). The access tract was embolized with a few coils or NBCA in order to prevent tract hemorrhage. Patients were kept in the hospital overnight for observation after the procedure.

In all patients, computed tomography (CT) volumetry was performed before and 3-6 weeks (median: 37 days; range: 17-71 days) after the procedure to measure TLV, FLV and tumor volumes. CT was performed with a 16-detector-row CT system (Sensation 16, Siemens Medical Systems, Erlangen, Germany). Volumetric data were obtained from the portal phase image. The CT volumetric calculation was acquired by calculating the volumes from the surface measurements, which were obtained from outlining the hepatic segmental contours and tumor contours in each slice at 5-mm intervals on a Workstation. TLV and FLR volume were calculated by subtraction of the tumor volume from each liver volume. The middle hepatic vein and gallbladder were used as markers to define the border between the right and left lobes of the liver. The caudate lobe was calculated as part of the left lobe because its portal vein branches were not embolized in most of the patients.

Complications were classified as major or minor according to the guidelines of the Society of Interventional Radiology Standards of Practice Com-

mittee (5). Major complications were defined as those necessitating major therapy, those necessitating an unplanned increase in the level of care or prolonged hospitalization (>48 h), and those resulting in permanent adverse sequelae or death. Minor complications were defined as those requiring no or nominal therapy, including overnight admission for observation only.

Changes in body temperature, serum total bilirubin (T-Bil) levels, liver enzyme levels including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and prothrombin time (PT) were analyzed in all patients before, 1 day after, 2-4 days after, and 1-2 weeks after PVE.

Resected specimens of the embolized lobes were examined to evaluate pathological findings of the hepatic parenchyma and portal vessels after PVE. Resected livers were fixed with formalin and sliced along parallel vertical or horizontal lines at 3-mm intervals. Hematoxylin-eosin-stained slides were reviewed, and the presence of tumor and adjacent non-tumor hepatic tissue was confirmed. Changes inside the portal vessels and in the hepatic parenchyma after PVE were examined.

All statistical analyses were performed using SPSS 15.0 statistical software (SPSS Inc., Chicago, IL, USA), with a *p* value <0.05 indicating statistical significance.

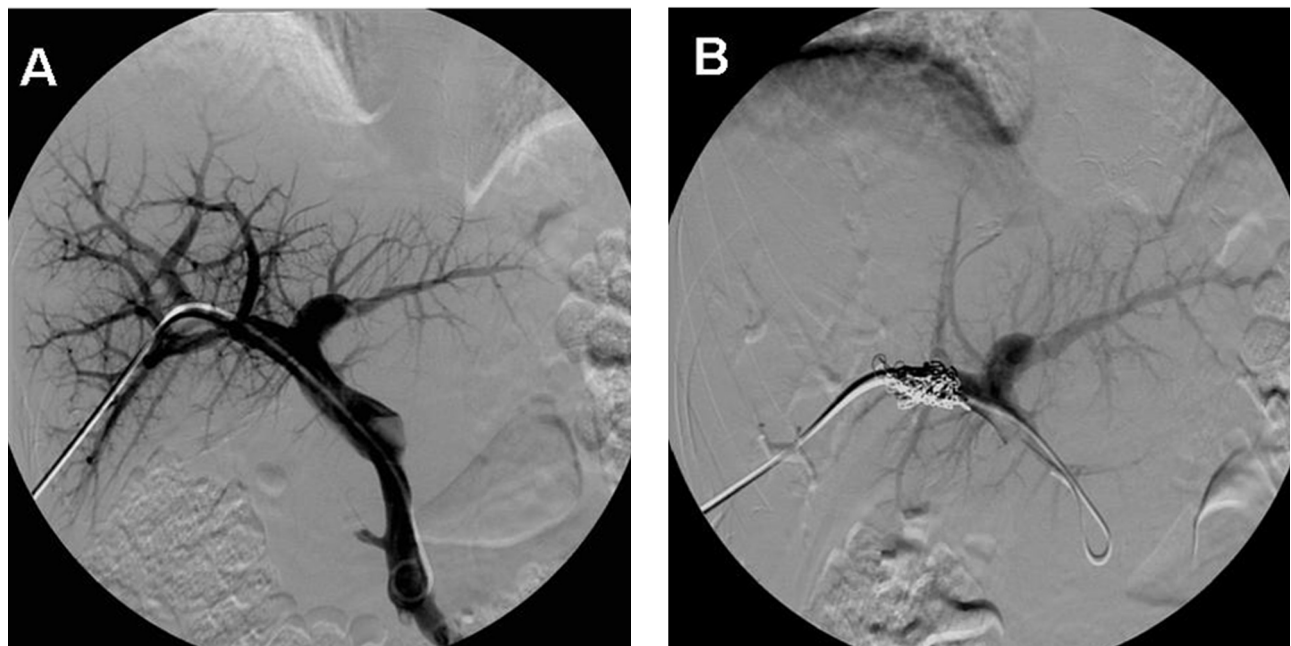


Figure 2. A, B: A 44-year-old woman with giant hemangioma. (A) Anteroposterior main portal venogram obtained before PVE of the right portal venous branches. (B) Portal venogram shows a total occlusion of the portal venous branches in the right lobe.

RESULTS

Portal vein embolizations (PVEs) were technically successful in all patients. Of all 20 patients who underwent PVE, the mean absolute FLR was measured as 326.7 cm³, which increased to a mean of 474.4 cm³ after PVE. The mean FLR/TLV ratio before PVE was 22.3%, and increased to 36% after PVE (Figures 3A, B). The mean increases in the absolute FLR volume and FLR/TLV ratio were 147.7 cm³ (range: 53 to 412 cm³) and 13.7% (range: 4.2 to 28.7%), respectively. The absolute FLR volume and FLR/TLV ratio after PVE were statistically significantly increased compared to those before PVE ($p < 0.003$, Wilcoxon test).

All patients tolerated the procedure well. There was no major complication related to the embolization procedure. Only one patient had asymptomatic partial main portal vein thrombosis detected on the one-month follow-up CT.

There was no statistical significance in the increase in the FLR/TLV ratio with respect to the embolic agents used. Cases embolized with alcohol showed a 13.5% increase, whereas cases embolized with other agents showed a 13.9% increase, with a p value of 0.93 (Mann-Whitney U test) (Table 1). However, all alcohol cases received general anesthesia instead of intravenous (IV) sedation. Furthermore, liver function tests were noted to be significantly altered in the alcohol group after the embolization. The most significant alterations in the blood tests were noted in AST, ALT and T-Bil levels (Table 2). However, all these liver function

Table 1. Differences in liver volume following embolization (emb)

	Pre-emb	Post-emb	Increase	P
FLR (ml)	326.7	474.4	147.7	<0.001
FLR/TLV Ratio (%)	22.3	36	13.7	<0.001
Alcohol group			13.5	0.93
Non-alcohol group			13.9	

FLR: Future liver remnant. TLV: Total liver volume.

Table 2. Differences in mean liver function parameters following PVE

	Pre-emb	Post-emb 2 days	Post-emb 14 days	P
AST (IU/L)	47	200	50	$p: 0.022$
Alcohol				$p > 0.05$
Non-alcohol	43	45	44	
ALT (IU/L)	40	170	42	$p: 0.006$
Alcohol				$p: 0.003$
Non-alcohol	37	50	38	
T-Bil (mg/dl)	1.2	1.8	1.2	$p: 0.029$
Alcohol				$p: 0.02$
Non-alcohol	0.6	1.1	0.6	

tests had returned to baseline levels 7-10 days after embolization. Only 8 patients had a $>1.0^{\circ}\text{C}$ increase in body temperature after PVE, returning to normal range with or without antipyretics within 3 days.

After PVE, although 5 of our patients had sufficient FLR, hepatectomies were cancelled because of peritoneal metastasis found at laparotomy in 2 pa-

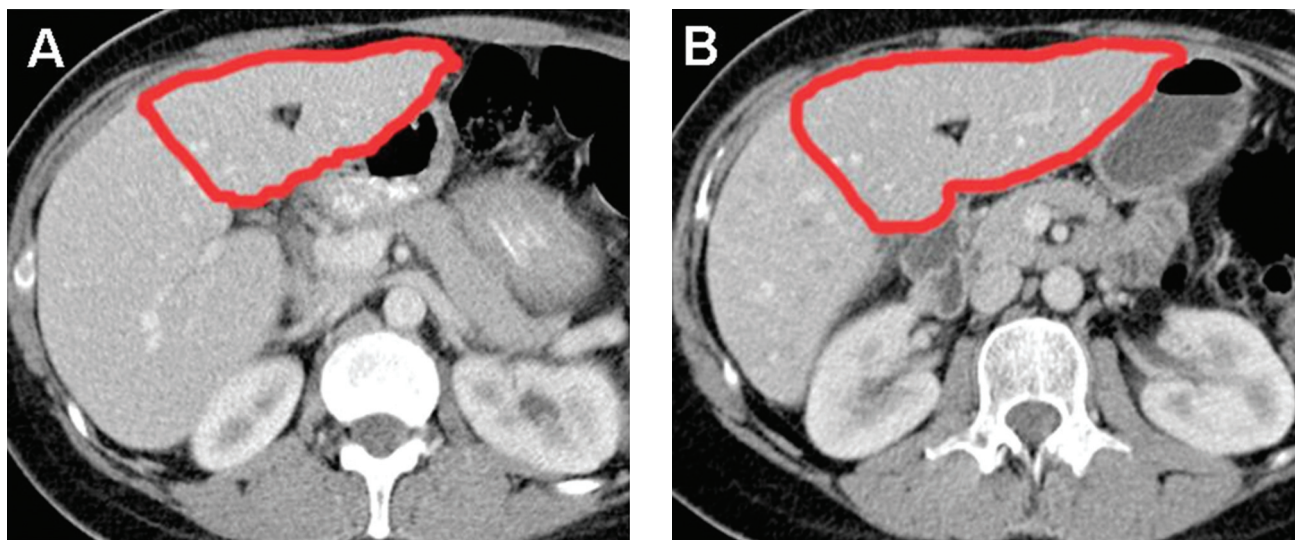


Figure 3. A, B: A 44-year-old woman with giant hemangioma. (A) Axial enhanced CT scans before PVE. (B) CT scan 6 weeks after PVE shows hypertrophy of the left lobe.

tients, new ovarian metastasis on follow-up CT after PVE in 1 patient, cerebrovascular incident in 1 patient, and prolonged infection in 1 patient not associated with PVE. Therefore, hepatectomies were performed in a total of 15 patients. The time from PVE to hepatectomies in these patients was 48 days (range: 24-85 days). Except for a biloma in 1 patient with giant liver hemangioma, no complication was seen related to the surgery. Biliary leak was again managed successfully during the follow-up with percutaneous drainage and catheterization. No hepatic failure was noted after the surgery.

In 1 case after the PVE procedure, since the FLR/TLV ratio was inadequate at the 6-week CT measurements, the operation was postponed. Seventy-one days after the PVE, the FLR/TLV ratio had finally increased and the patient underwent successful resection. In another patient with history of coronary artery disease, diabetes and alcohol abuse, a second PVE procedure was needed since the FLR/TLV ratio only rose to 20.7% after the first embolization. He was operated 6 weeks after the second session when the ratio increased to 30.8%.

Although the primary goal of our study was to assess the success rate of the PVE procedure itself with different embolic agents, recurrence rates was also evaluated retrospectively. A total of 5 of

6 HCC cases and 7 of 11 metastatic colon cancer cases underwent successful surgical resection after PVE. Among these patients who underwent successful resection, recurrence in the remnant liver was detected in 2 of 5 (40%) patients with HCC and 1 of 7 (14%) patients with colon cancer during the 18-month follow-up.

Pathologic Examination

Necrosis or degeneration was found in specimens from the hepatic parenchyma. In areas with extensive embolization, the hepatic parenchyma showed more massive coagulation necrosis and organized embolus, which included PVA, iodized oil and fibrosis with lymphocytic and eosinophilic infiltration within the portal vein (Figures 4A, B). There were early cirrhotic changes in the pathological examinations of 3 of 5 patients with HCC who underwent successful surgical resection after PVE.

DISCUSSION

Improvement in the techniques of liver resection and better peri-operative care make major liver resection more feasible and safe. However, postoperative liver failure still occurs, sometimes leading to death, especially when the resection has left only a small liver remnant. To expand surgical eligibility, PVE has been increasingly used to faci-

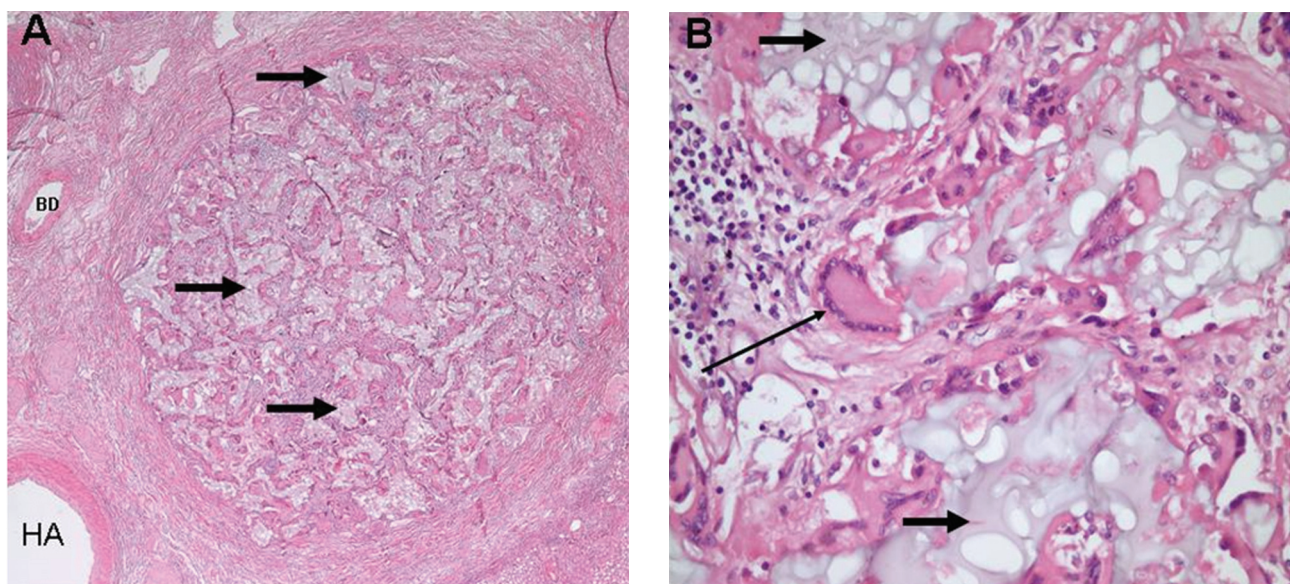


Figure 4. A, B: A 52-year-old woman with metastatic stomach carcinoid. **(A)** Low-power (x40) and **(B)** high-power (x400) photomicrographs with hematoxylin and eosin stain show the histologic features of PVA particles in resected liver specimens after right PVE with PVA particles. The amorphous PVA particles (thick arrows) with prominent foreign-body giant-cell reaction (thin arrow) are predominantly distributed in a large PV branch. HA: Hepatic artery. BD: Bile duct.

litate major hepatic resection by decreasing the risk of postoperative liver failure. Numerous studies have shown PVE to be safe and efficacious for producing hypertrophy with a low risk of postoperative liver failure (1,2,6-10). A recent meta-analysis found the overall morbidity rate for PVE to be 2.2% with no mortality, and a <1% rate of fatal liver failure after hepatectomy (11).

Although a FLR/TLV ratio of at least 25% in normal patients and of 40% in those considered to have compromised liver (e.g., from chronic liver disease or high-dose chemotherapy) is recommended (12), in a recent study, these rates were revised to 29.8% and 35.3%, respectively (13). In our study, the mean FLR/TLV ratio before PVE was 22.3%, meaning that all cases had an indication for PVE according to the literature.

The demonstrated increase of 13.7% in the FLR volume after PVE in this study is comparable with the other literature (range 6%-14%). No significant differences among the various embolic materials used could be found, including in our study.

The mean time from PVE to CT was 37 days in our study and from PVE to hepatectomy was 48 days. Liver regeneration is usually most active during the first three weeks after PVE, and then more slowly thereafter (1). In many studies, the reported time from PVE to hepatectomy was 4–6 weeks (10). Our mean time from PVE to hepatectomy is longer than the literature intervals because of the patients' conditions. We believe that, if this interval could have been shortened, more of our patients would have had subsequent resection.

Portal vein embolization (PVE) with stem cell administration is reported to be a promising technique that augments preoperative liver regenerati-

on and shortens the time interval between embolization and surgery. In this technique, stem cells are applied to the FLR segments via a diagnostic catheter 2–4 hours after PVE (28,29). Fürst et al. (29) reported that the time to surgery of patients who underwent PVE and stem cell administration decreased approximately 18 days.

There are a number of studies reported in the literature on PVE with different embolic materials including cyanoacrylate, gelatin sponge, coils, PVA, and absolute alcohol (4,14-25). In comparison of selected reports with our study group, our rate of increase in FLR is superior (Table 3). Absolute ethanol is a very strong embolic agent and probably the cheapest among the agents used for PVE. However, the literature reports only minimal and insignificant differences with respect to rates and degrees of hypertrophy of FLR according to the different agents used (26,27). In our study, there was no statistically significant difference in degrees or rates of hypertrophy of FLR between alcohol and the other embolic agents. Therefore, from our standpoint, the need for general anesthesia when using alcohol cannot be justified for PVE.

The incidence of major complications related to PVE is 0–15% in the literature (4). After PVE with various embolic materials, signs and symptoms of postembolization syndrome, such as nausea and vomiting, are rare. Fever and abdominal pain are minimal as well. Changes in liver functions detected biochemically after PVE are reported to be minor and transient. When transaminase levels rose, they peaked at a level less than three times of baseline from 1 to 3 days post-PVE. They then returned to normal levels after 7-10 days. PT was rarely affected. Although ethanol has the greatest impact on liver function, it is usually minor and transient

Table 3. FLR volume change following right PVE with various embolic agents

Authors, year	Embolic agents	No. of patients	Increase FLR/TLV (%)
De Baere et al. 1996 (16)	NBCA	24	13
Imamura et al. 1999 (17)	Gelatin sponge powder, thrombin	84	10.2
Kakizawa et al. 2006 (19)	Gelatin sponge, iodized oil	14	7.9
Azoulay et al. 2000 (21)	NBCA, iodized oil	30	11
Covey et al. 2005 (22)	PVA	39	9
Ji et al. 2003 (23)	Ethanol, iodized oil	23	10.7
Madoff et al. 2003 (25)	PVA, coil	26	7.7
Shimamura et al. 1997 (26)	Ethanol, iodized oil	19	11.4
Our study	Alcohol group	10	13.5
	Non-alcohol group	10	13.9

FLR: Future liver remnant. TLV: Total liver volume. NBCA: N-butyl cyanoacrylate. PVA: Polyvinyl alcohol.

(4,10,19,24,26). In our study, no obvious major complications were seen. However, one patient had asymptomatic partial main portal vein thrombosis detected on the one-month follow-up CT. PT remained normal in all patients in our study.

Our experience suggested a higher recurrence rate in patients with HCC after surgery compared to the patients with liver metastasis of colon cancer. This is expected data, as the underlying liver disease is mainly responsible for HCC in patients with chronic liver disease. For the same reason, it is widely accepted that liver transplantation is superior to resection because of lower recurrence rates. On the other hand, the literature data about HCC in non-cirrhotic livers favors resection, as the

five-year survival is around 50% and significantly superior to that of the patients with underlying cirrhosis (30). Further studies are warranted on resection versus transplantation in HCC patients with both cirrhotic and non-cirrhotic livers.

In conclusion, despite the limited patient number and retrospective study design of our study, no statistical differences were noted between alcohol and the other embolic agents with respect to FLR increase. According to our experience, time intervals between embolization and surgery should be kept as short as possible in order to avoid other potential complications of the embolization procedure, co-morbid problems and the underlying primary liver disease.

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