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Portal Vein Embolization Using a Histoacryl/Lipiodol Mixture before Right Liver Resection

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Key Words
Portal vein embolization · Histoacryl/Lipiodol mixture · Liver lobe volume

Abstract
Purpose: The purpose of this retrospective study was to evaluate the efficacy and safety of percutaneous transhepatic portal vein embolization (PVE) of the right liver lobe using Histoacryl/Lipiodol mixture to induce contralateral liver hypertrophy before right-sided (or extended right-sided) hepatectomy in patients with primarily unresectable liver tumors. ***Methods:*** Twenty-one patients (9 females and 12 males) underwent PVE due to an insufficient future liver remnant; 17 showed liver metastases and 4 suffered from biliary cancer. Imaging was performed prior to and 4 weeks after PVE. Surgery was scheduled for 1 week after a CT or MRI control. The primary study end point was technical success, defined as complete angiographical occlusion of the portal vein. The secondary study end point was evaluation of liver hypertrophy by CT and MRI volumetry and transfer to operability. ***Results:*** In all the patients, PVE could be performed with a Histoacryl/Lipiodol mixture (n = 20) or a Histoacryl/Lipiodol mixture with microcoils (n = 1). No procedure-related complications occurred. The volume of the left liver lobe increased significantly ($p < 0.0001$) by 28% from a mean of 549 ml to 709 ml. Eighteen of twenty-one patients (85.7%) could be transferred to surgery, and the intended resection could be performed as planned in 13/18 (72.3%) patients. ***Conclusion:*** Preoperative right-sided PVE using a Histoacryl/Lipiodol mixture is a safe technique and achieves a sufficient hypertrophy of the future liver remnant in the left liver lobe.

Introduction

Liver resection has been commonly assumed to be the gold standard treatment for advanced primary or secondary liver malignancies. It is the only curative therapeutic approach, but extensive resection of liver parenchyma increases the risk of postoperative hepatic dysfunction up to hepatic failure [1–5].

Patients with normal liver parenchyma can tolerate a resection of 75% of the total liver volume without a significant increase of postoperative hepatic failure, whereas in patients with underlying liver disease (e.g. liver cirrhosis or after chemotherapy) resections of 60–70% of the total liver volume were found to be safe [6–8]. In patients who would otherwise be good candidates for hepatic resection, the lack of adequate future liver remnant may be the only obstacle.

Hypertrophy of the left liver lobe occurs a few weeks after embolization of the right-sided portal veins, as a result of the regenerative capacity of the liver [9–12]. The

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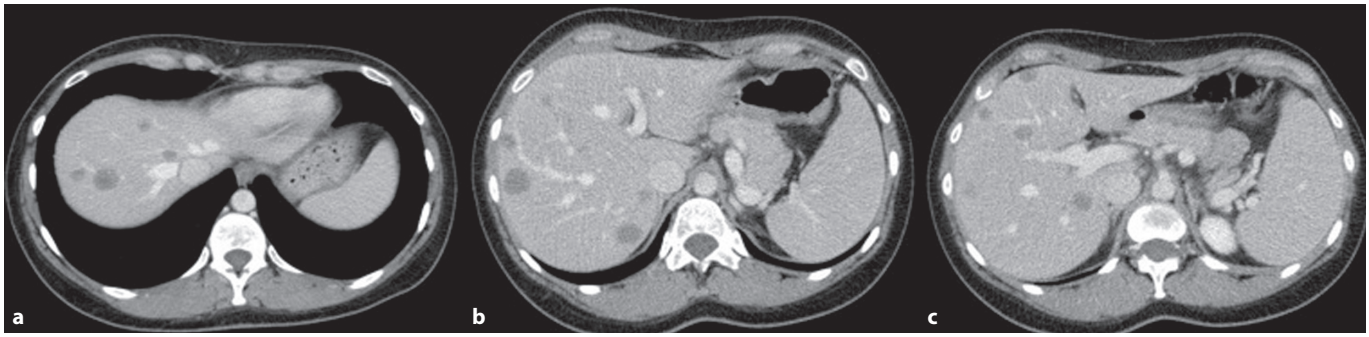

Fig. 1. Contrast-enhanced CT (venous phase 3-mm slice) in a young female with rectal cancer. **a** Visualization of multiple liver metastases in the right liver lobe with a maximal diameter of 3 cm. **b**, **c** The extra- and intrahepatic portal vein can be delineated without thrombosis. 331 × 80 mm (300 × 300 DPI).

increase in remnant liver volume has been reported to be 8–64% at various follow-up periods [9–11, 13–16]. The hypertrophy of the residual liver volume reduces the risk of postoperative organ failure and overall postoperative morbidity. Nowadays, portal vein embolization (PVE) is a widely used minimally invasive interventional procedure to improve the outcome of major liver resection and transfers initially unresectable patients into operable cases [11, 17].

Contraindications for PVE are portal vein thrombosis, unresectable extrahepatic metastases and acute liver and renal failure.

Various different embolic agents (particles like polyvinyl alcohol, absorbable gelatin sponges or microspheres, liquid embolic agents like absolute alcohol, thrombin or Ethibloc and metallic material like coils or the Amplatzer vascular plug) have been used for PVE. Our preferred embolic agent was Ethibloc (Ethicon, Germany), which is no longer available. On account of good experiences with Histoacryl in the preoperative embolization of renal carcinomas, we chose this material for PVE. The aim of this retrospective study was to evaluate the technical success of PVE of the right liver lobe with a Histoacryl/Lipiodol mixture in patients with primarily unresectable liver tumors as primary study goal. The secondary study goal was the evaluation of contralateral liver hypertrophy by CT or MRI volumetry and the transfer to operability.

Materials and Methods

Patients

Between June 2007 and August 2010, 21 patients underwent percutaneous transhepatic right PVE at our institution prior to (extended) hemihepatectomy using a Histoacryl/Lipiodol combination. The indication for PVE was established individually for each patient by radiological-surgical consensus. Preoperative PVE was indicated in patients with compromised liver function when the anticipated volume of future liver remnant was <40% of the total liver volume, and <25% in patients with normal liver function.

Preprocedural and Postprocedural Imaging

In all patients, volumetry using CT or MRI was performed before and after PVE.

According to the study protocol, imaging was performed 4 weeks after PVE in all patients. Surgery was then performed 1 week after the CT control. Most of the patients were routinely examined by 64-row multidetector CT scan (Somatom Definition, Siemens, Erlangen, Germany) and 3-phase (nonenhanced, arterial and venous phase) CT images were obtained (fig. 1). After the nonenhanced phase, 120 ml iodinated contrast medium (Ultravist-370 Bayer Vital; Leverkusen, Germany) was injected with an automated injector with a flow rate of 5 ml/s. The venous phase was started after a delay of 40 s. The entire abdomen was scanned and axial and coronal reformations with 3-mm slice thickness were reconstructed and analyzed.

The images before the interventional procedure provided information regarding the number and location of the liver metastases/biliary cancers and the patency of all liver vessels as well as the resectability criteria, based on the evaluation of vascular relationships ensuring adequate perfusion.

After routine examination, the same protocol was used for the assessment of liver volume changes (fig. 2).

Patients with known allergic reactions after treatment with iodized contrast material or lack of availability were examined in external MRI before the interventional procedure.

All patients underwent measurement of total liver volume and volume of the right and left liver lobe both before and after PVE by CT or MRI volumetry. Total, right hemi and left hemi liver volumes were calculated before and after embolization with manual and semiautomated segmentation techniques of

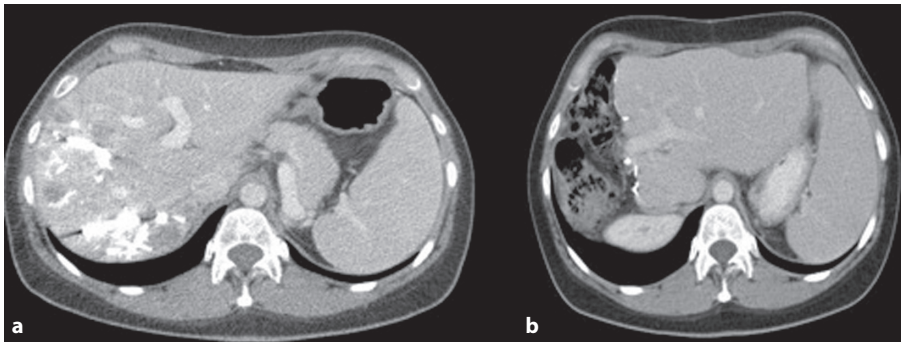

Fig. 2. **a** Total occlusion of the right-sided portal venous system 30 days after embolization with Histoacryl/Lipiodol. **b** The same patient 9 months after right-sided hemihepatectomy shows a massive hypertrophy of the residual liver. 212 × 80 mm (300 × 300 DPI).

the portal-phase images for volumetric calculations (Aquarius NET Viewer 4.4.4.23, TeraRecon Inc., Germany). A manual technique was used to outline the perimeter of the liver, excluding the gallbladder and the inferior vena cava on each section, and the enclosed area was measured. Tumor volume was included in the calculations. The middle hepatic vein and the gallbladder were used as landmarks to define the border between the right and left liver lobes.

Material and Embolization Technique

PVE was performed as an inpatient procedure after monitored analgosedation using intravenously administrated midazolam (1.25 mg; Hoffmann La Roche, Germany) and 75 mg of pethidine (Aventis Pharma, Germany). In a standardized technique under CT guidance, the percutaneous puncture of the portal vein was performed with a 20-cm, 22-gauge Neff needle (Cook, USA) [12]. We have had good experiences with CT-guided biopsies and punctures, so we did not use fluoroscopic or ultrasound-guided punctures. The next intervention was carried out in the angiography suite. A 0.46-mm platinum wire was inserted via the needle into the portal vein retrogradely in order to position a 5-Fr introducer sheath. The wire and the introducer sheath pusher were then removed once it had been observed that the sheath was positioned correctly in the portal vein.

After inserting a steerable 0.035-in stiff Terumo guidewire (Radiofocus, Terumo Japan), a 4-Fr Berenstein catheter was established in the main stem of the portal vein. The introducer sheath was removed and a 4-Fr pigtail catheter was placed (Royal Flush Plus, Cook, USA) in the main stem of the portal vein for portography.

After analysis of the anatomy of the right-sided portal vein, a 4-Fr Vertebralis (Terumo Europe, Belgium) or Berenstein catheter was positioned in the posterior right-sided pedicle of the portal vein, and then a 2.7-Fr Progreat Terumo microcatheter (Terumo Europe) was put in the distal vessel and embolization was performed while pulling the catheter.

The target branches of the right portal vein were embolized with a mixture of Histoacryl/Lipiodol (Boston Scientific, USA/Byk Gulden, Germany) (fig. 3).

Technical success was defined as the final occlusion of all vessels supplied by the portal vein excluding the proximal 2 cm of the feeding main portal. We excluded the proximal part of the feeding main portal to enable the surgeons to place a clamp without displacement of embolic material.

Statistics

All data were expressed as mean ± standard deviation (SD). A nonparametric matched-pairs test (the Wilcoxon signed-rank test) was used to compare the volumetric data between the groups. Statistical analysis was performed using the GraphPad Prism package version 4.0c (GraphPad Software Inc., USA) with a p value of <0.05 indicating statistical significance.

Results

Patients

Twenty-one patients (9 females and 12 males) with a mean age of 61 ± 12.4 years (range 35–81 years) were in the study population. Of these, 17 had liver metastases, 12 had colorectal cancer, 3 had a neuroendocrine pancreas tumor, 3 had gastrinoma, 1 had renal cancer and 4 had biliary cancers [Klatskin tumors Bismuth IIIb (n = 1) and IV (n = 3)].

One patient (4.8%) with colorectal metastases had previously undergone percutaneous transarterial chemoembolization of the right liver lobe, a second had had radiofrequency ablation of a metastatic lesion (also in the right liver lobe) and a third had had a surgical resection of liver segments 7 and 8. Eight patients (38.1%) with colorectal metastases had undergone chemotherapy and 2 (9.5%) had undergone a combined radiochemptherapy. Liver fibrosis as an underlying liver disease, detected by preoperative biopsy, was seen in 2 patients (9.5%) as well as hepatitis B in 1 patient (4.8%).

Technical Success

The PVE procedures were technically successful in all of the patients. In 20 patients (95%) a contralateral CT-guided approach was carried out and 1 patient (5%) an ipsilateral puncture, because of a small left hemi liver and

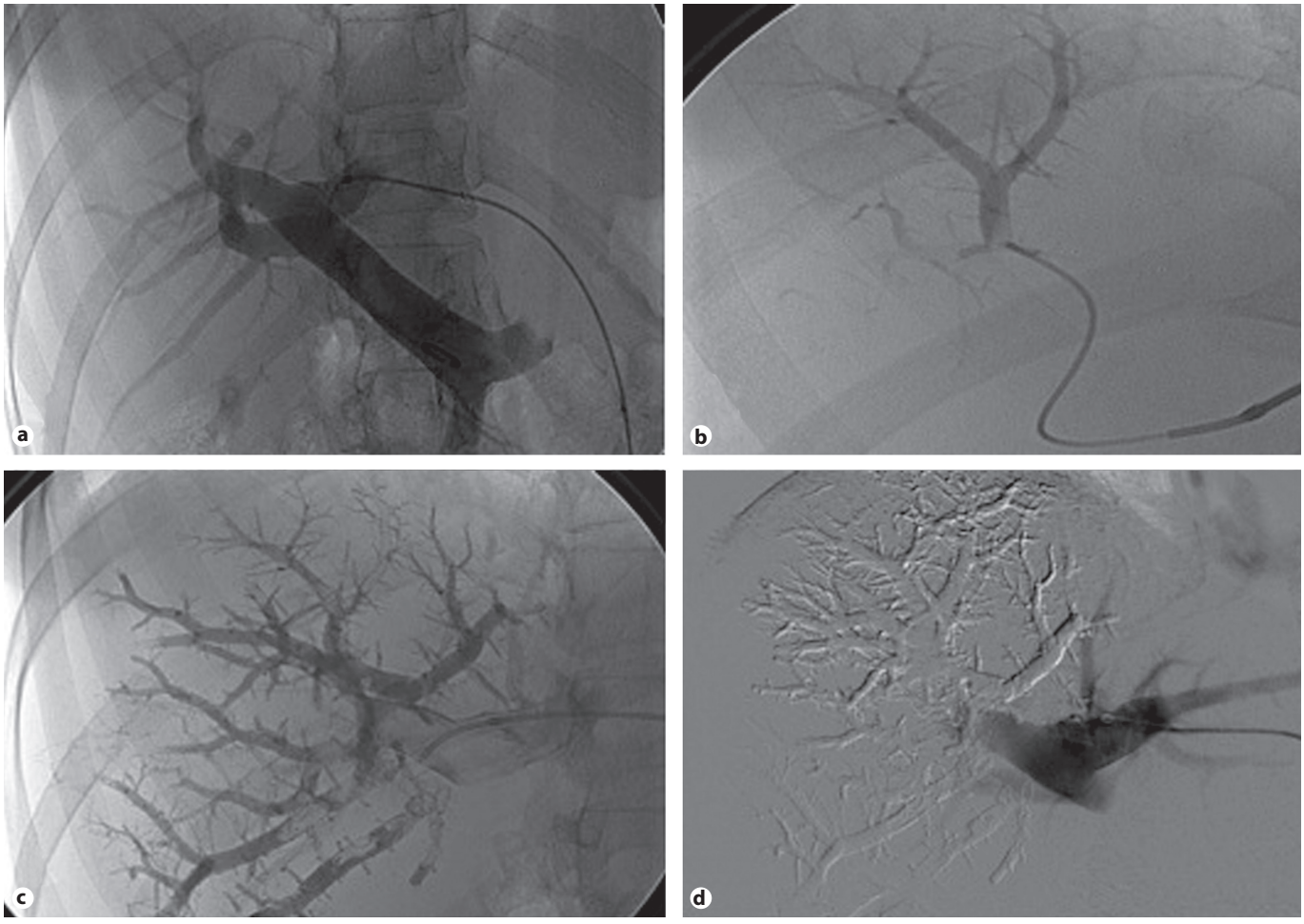

Fig. 3. **a** Placement of a pigtail catheter in the main portal branch after CT-guided puncture of the left portal vein. **b** Catheterization of a right-sided portal branch via a microcatheter system. **c**, **d** Visualization of the entire embolized area of the right-sided portal branches. 228 × 160 mm (300 × 300 DPI).

the absent of parenchymal coverage. The target branches of the right portal vein were embolized with a mixture of Histoacryl/Lipiodol alone with a mean ratio of 1:4 (dependent on the end point; range 1:1–1:5) in 20 patients, and a combination of Histoacryl/Lipiodol with microcoils was used in 1 patient until complete occlusion of the right-sided portal vein system was achieved. The mean volume of Histoacryl/Lipiodol was 6.6 ± 4.1 ml (range 2–15 ml). The fluoroscopy time was 17.1 ± 8.9 min (range 6.1–31.3 min) on average, with a mean radiation dose of 194.6 ± 127.7 Gy/cm^2 (range 24–449 Gy/cm^2).

Volumetry

The volume of the left liver lobe after embolization of the contralateral liver lobe at follow-up after 30 days (median) had significantly increased by a mean of 28% (+2.3 to +70.0%) from a mean of 549 ml (296–1,029 ml) to 709 ml (380–1,517 ml) ($p < 0.0001$) (table 1).

At the same time, there was an insignificant decrease in the volume of the right liver lobe by a mean of 4.4% (–23.1 to –28.2%) after embolization from a mean of 1,205 ml (817–2,186 ml) to a mean of 1,130 ml (628–1,816 ml) ($p = 0.0551$). There was not a significant increase (mean 5.1%; –13.3 to +26.3) in the total volume of the liver from a mean of 1,754 ml (1,216–2,697 ml) to a mean of 1,830 ml (1,293–2,849 ml) ($p = 0.1840$).

The ratio of residual liver/total liver volume increased by a mean of 23.3% (–7.4–61.1%) from a mean of 31.6% (18–45%) to a mean of 38.4% (22–55%). After PVE, complete occlusion of the portal veins was achieved in

Table 1. Relative liver volumes before and after PVE

Left liver lobe volume before PVE (ml)	Left liver lobe volume after PVE (ml)	Hypertrophy ratio left lobe (%)	Total liver volume before PVE (ml)	Total liver volume after PVE (ml)	Increase in left lobe/ total liver volume (%)
549.4 (296–1,029)	708.6 (380–1,029)	28 (2.3–70)	1,754 (1,216–2,697)	1,830 (1,293–2,849)	23.27 (–7.4–61.1)

all patients with no detection of portal venous recanalization in the CT after a median of 30 ± 25.1 days (range 16–132 days).

Complications and Postinterventional Follow-Up

No embolization-related acute liver failure occurred. No patient experienced puncture-site complications, such as hematoma, portal vein thrombosis, infections, cholangitis or pneumothorax.

One patient (4.8%) developed fever within 24 h of the embolization procedure and 2 (9.5%) exhibited persistent abdominal pain. All patients were discharged from the hospital after a median of 3.0 ± 0.8 days after embolization (range 2–5 days).

Surgery/Liver Resection

Out of 21 patients, 18 (85.7%) underwent surgery a median of 36.0 ± 16.8 days (range 21–89) after PVE. Hemihepatectomy was feasible in 13 of these 18 (72.3%); this included an extended right-sided hemihepatectomy in 6 (46.2%) and a right-sided hemihepatectomy in 7 (53.8%). R0 resection was achieved in 9 patients (69.2%), R1 in 3 (23.1%) and R2 in just 1 (7.7%).

Five patients (23.8%) underwent an exploratory laparotomy only, due to intraoperative findings [irresectable tumor/intrahepatic metastases (n = 3) or peritoneal carcinomatosis (n = 2)]. Three patients (14.3%) did not even undergo an exploratory laparotomy because of insufficient hypertrophy of the left liver lobe and/or progressive metastases 33 days (range 28–41 days) after PVE.

Three patients (16.7%) suffered from perihepatic abscesses after surgery. Unfortunately, 2 patients (11.2%) died after extended right-sided hemihepatectomy due to liver failure and other complications (e.g. respiratory failure). No transient liver failure occurred after surgery.

Following surgery, patients were discharged after a median of 15.0 ± 19.6 days (range 8–77 days).

In 2 patients with insufficient hypertrophy, 39 and 46 days after PVE, respectively, an Amplatzer vascular plug (AGA Medical, Germany) was placed over a transjugular approach into the right hepatic vein to occlude it and to induce further hypertrophy of the left liver. In one of these 2 patients, after technically successful PVE but with insufficient hypertrophy even after the placement of the Amplatzer device, no operation was feasible due to insufficient hypertrophy of the left liver lobe and the occurrence of new metastases in the future liver remnant. The second patient showed sufficient hypertrophy and was transferred to surgery; however, a surgical resection proved not feasible due to the intraoperative detection of distant peritoneal metastases.

Discussion

Percutaneous transhepatic PVE is an established strategy to reduce the risk of liver dysfunction or failure after (extended) hemihepatectomy. First described in humans in the early 1980s, this procedure has become a widely accepted preoperative method in an effort to increase the number of operable patients among those who are candidates for hepatic resection [11, 15]. The occlusion of portal branches comprises a 2-fold effect: atrophy of the embolized parenchyma and hypertrophy of the unembolized parenchyma. Previous study findings have suggested that 40% of the total liver volume must be preserved in patients with a liver that has been damaged by chemotherapy or underlying liver diseases e.g. liver cirrhosis. The hypertrophy rate of the unembolized liver segments is variable and depends on the underlying liver disease and systemic diseases [3].

Various embolic agents have been used for the preoperative PVE of liver metastases or malignant liver tumors and there is still a debate regarding the optimal embolic material [18–20]. Because our previous preferred embolic agent Ethibloc was no longer available, we chose Histocryl as a replacement, because of many years of experience with the use of a Histoacryl/Lipiodol combination in the preoperative embolization of renal carcinomas.

Similar to Ethibloc, Histoacryl is used in a mixture with Lipiodol and leads to total and permanent occlu-

Table 2. Overview of the current literature

Authors	Year	Embolization material	Number of patients	Complications	Liver metastases/ HCC/CCC	Hypertrophy residual liver	Increase in ratio: residual liver lobe/ total liver volume
Madoff [3]	2003	PVA/coils	26	7.7%	Liver metastases/HCC/CCC	8.0%	41.1%
Covey AJR	2005	PVA	58	0%	Liver metastases	24.3–31.9%	9–10.0%
Radeleff [12]	2008	Ethibloc/Lipiodol	14	14.3%	Liver metastases/HCC/CCC	28.3%	27.1%
Our study	2010	Histoacryl/Lipiodol	21	0%	Liver metastases /CCC	28.0%	23.3%

CCC = Cholangiocellular carcinoma; HCC = hepatocellular carcinoma; PVA = polyvinyl alcohol.

sion of the embolized area, as has been demonstrated by follow-up CT scans. Furthermore, Lipiodol is used to control the precipitation; with a mixture of 1:4, we can achieve a deep capillary embolization without risking recanalization. Other advantage of Histoacryl are its syringeability through a microcatheter in combination with glucose and being able to use it independently according to the clotting situation.

A disadvantage is the difficult application with the risk of failed embolization. Early polymerization with the risk of occlusion of the microcatheter must also be discussed.

Liver Hypertrophy after PVE

There are variable data about the increase of the residual liver parenchyma volume ranging from 13 to 127% [21, 22] (table 2). This variability can be explained by the use of different embolic agents, varying intervals between the embolization and the operation and/or varying stages of liver function before an intervention.

In this study, we observed a significant increase of 28% (from mean of 549 to 709 ml) in the volume of the left liver lobe after PVE, which is comparable to one of our previous studies that showed an increase of 28.3% with our standard Ethibloc/Lipiodol mixture [12].

Finally, we were able to transfer 18/21 (85.7%) patients into operability. The planned operation was feasible in 13/18 (72.3%) patients, which was equivalent to our previous study where it had proved feasible in 11/13 (81.8%) patients.

The use of Amplatzer vascular plugs showed a satisfying result only in 1 of 2 patients. A second study with a larger study population would be required to evaluate the efficacy in achieving an additive hypertrophy of the contralateral liver lobe using these plugs. Yamanaka et al. [23] reported that the regeneration process of normal liver parenchyma after surgical resection occurs in 3 phases: a rapid increase was seen during the first month, a decrease during the second month and finally a slow increase. This variability in the increase of volume could be due to the varying intervals between PVE and surgery as well as different embolic agents and varying preinterventional stages of liver disease and function.

The complication rate found in recent literature lies between 9 and 15%, including pneumothorax, subcapsular hematoma, pseudoaneurysm, hemobilia and portal vein thrombosis [24, 25]. We found no procedure-related complications in our study.

Moderate symptoms of postembolization syndrome, i.e. fever, nausea, leukocytosis and elevated values of CRP were present in most of the patients.

The limitations of this study are its retrospective nature and the small study population. A larger prospective study with a longer follow-up period is needed to confirm our findings.

Conclusion

Preoperative PVE with Histoacryl/Lipiodol mixture is a safe and successful method resulting in compensatory hypertrophy of the unembolized liver.

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