

Improved Hypertrophy of Future Remnant Liver after Portal Vein Embolization with Plugs, Coils and Particles

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Abstract

Purpose To retrospectively analyze efficacy as measured by volume gain of future remnant liver (FRL) after right portal vein embolization (PVE) using particles only versus particles and additional central plug and/or coil (CP/C) embolization.

Methods All patients who underwent PVE between July 2011 and December 2012 were retrospectively analyzed. Right PVE was performed either with particle-only (PO) embolization or additional CP/C embolization. All enrolled patients underwent computed tomography or magnetic resonance imaging before PVE and surgery. The images were used for volumetry of the FRL.

Results Of 75 patients, 40 had PO and 35 CP/C embolization. Age, sex, and tumor entities did not differ significantly between the two groups. Tumor entities included cholangiocarcinoma ($n = 52$), metastasis from colorectal cancer ($n = 14$), hepatocellular carcinoma ($n = 2$), and others ($n = 7$). Time from PVE to preoperative imaging was similar in both groups. FRL volume before PVE was 329 ± 121 ml in the PO group and 333 ± 135 ml in the CP/C group, and 419 ± 135 ml and 492 ± 165 ml before

operation. The average percentage volume gain was significantly higher in the CP/C group than in the PO group, with 53.3 ± 34.5 % versus 30.9 ± 28.8 % ($p = 0.002$).

Conclusion Right PVE with additional CP/C embolization leads to a significantly higher gain in FRL volume than embolization with particles alone.

Keywords Future remnant liver · Hypertrophy · Portal vein embolization · Vascular plug · Volumetry

Introduction

In the last few decades, technical advances in hepatobiliary surgery have improved perioperative outcome in patients undergoing major hepatic resection [1]. One major development is extensive right liver resection for hilar cholangiocarcinoma and other primary and secondary malignancies in critical localization, affecting the right liver, including segment IV. This strategy allows radical tumor removal and improved recurrence-free and overall survival [2–4]. Postoperative outcome depends—among other things—on the remaining liver volume or future remnant liver volume (FRLV) as morbidity increases when the FRLV in non-cirrhotic patients is less than approximately 25 %, and morbidity and mortality increase when the FRLV is less than approximately 40 % of the total liver volume (TLV) in patients with parenchymal disease [5–8]. Moreover, combining measured volume with functional assessment using the innovative LiMax test allows assessment of the more important future remnant liver (FRL) function for estimation of individual risk and point-of-care treatment [9, 10]. To improve postoperative outcome and to increase the number of resectable tumors, preoperative portal vein embolization (PVE) has become an established strategy in patients in

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whom the expected FRLV or FRL function is critical. First described in the 1920s, portal vein occlusion leads to a compensatory hypertrophy of the contralateral lobe [11], and therefore embolization of the right portal vein facilitates safe extended right hemihepatectomy after a growth interval of approximately 3–6 weeks [12–19].

Portal vein embolization is performed using a percutaneous transhepatic or intraoperative transileocolic approach. The transileocolic route requires a laparotomy and is therefore used in only approximately 12 % of published cases [15]. Percutaneous transhepatic PVE simply requires ipsilateral or contralateral portal venous puncture; most centers prefer the ipsilateral access in order to avoid vascular complications in the remaining liver lobe [15]. The materials preferably used for PVE are polyvinyl alcohol (PVA) particles, gelatin sponge, fibrin glue, *n*-butyl cyanoacrylate (NBCA) with lipiodol, polydocanol foam, or combinations of these materials with coils or Amplatzer vascular plugs (AVP). A systematic review by van Lienden et al. [15], shows that gelatin sponge and *n*-butyl cyanoacrylate are the most widely used materials. They are increasingly combined with central plug and/or coil (CP/C) embolization. One reason is the suspected lower rate of reperfusion leading to a decreased hypertrophy. Another reason is the embolization of segment I, which may sometimes be achieved by central occlusion. However, to our knowledge, there are no clinical studies that compare the effect of different embolization materials on the hypertrophy response [8, 20]. Therefore, the aim of this retrospective study was to analyze the volume gain of the FRL after right PVE in patients who received particle embolization alone compared to patients who received additional CP/C embolization.

Methods

All consecutive patients who underwent PVE between July 2011 and December 2012 were included in our study. All patients were presented to and discussed by an interdisciplinary tumor board, which approved the indication for extended right hemihepatectomy and PVE. The study complied with the Declaration of Helsinki. The study protocol was approved by the institutional review board.

Portal Vein Embolization

Portal vein embolization was performed by using a percutaneous transhepatic access established ipsilaterally via ultrasound- or computed tomography (CT) fluoroscopy-guided direct puncture (21-gauge coaxial needle, 15 cm long; Cook Medical, Bloomington, IN, USA) of a right intrahepatic portal vein (PV) branch. Intraoperative, transileocolic access and consecutive particle-only (PO)

embolization was used in one case. A 0.018-inch guide wire was advanced through the needle into the superior mesenteric vein or the splenic vein. The 0.018-inch guide wire was replaced by a stiffer 0.035-inch wire (0.035-inch Safe-T-J-curve; Cook Medical, Bloomington, IN, USA) over a dilatation system (AccuStick II; Boston Scientific, Natick, MA, USA). Over the 0.035-inch guide wire, a tip-marked 4F angiography sheath (23-cm length, opaque tip; Brite-tip sheath; Cordis, Bridgewater, NJ, USA) was introduced in the main PV. Direct portography was performed to visualize PV anatomy. A reverse catheter (Sidewinder 1 tempo; Cordis Corporation, Warren, USA) with a 0.038-inch inner diameter was used to achieve ipsilateral access to the right portal venous system. Branches of right PV were selectively catheterized, and embolization was performed with increasing sizes of PVA particles (250–1,000 μm Contour, Boston Scientific, Natick, MA, USA) until stasis was achieved. In the plug and/or coil group, an AVP type I or II with a diameter of 10–18 mm (St. Jude Medical, St. Paul, MN, USA) and/or large coils (Tornado or Nester Coils 6–10 mm in diameter, Cook Medical, Bloomington, IN, USA) were used to seal the entry of the right main branch or branches. In case of need for clamping of the right main PV during surgery before PV resection, we left the first centimeter after branching of the left PV without plug or coil material. In cases with long enough right PV, a plug was placed. If the right PV was too short for plug placement, coil embolization was performed. Additional coil embolization was necessary in some cases, when no complete thrombosis of the plug was visible after 10 min. In coil-only embolization, the coil embolization could be performed over the 0.038 Sidewinder I catheter. In case of plug embolization, the sheath had to be replaced by a 7F or 8F sheath. We decided to take a sheath diameter one French larger than recommended by the manufacturer to allow the parallel placement of a 3F Pigtail catheter with 4 side holes (C3F70P, BALT, Montmorency, France) in the main PV. With this 3F pigtail, the occlusion of the plug could be controlled at any time.

In cases where segment 4 PV branches arise from the left PV, these branches were not selectively embolized because the left PV system was not accessed unless the PV of the right anterior segment originated from the left PV. The success of PVE was controlled by direct portography either of the 4F sheath or over the 3F pigtail catheter. If embolization was still incomplete, larger particles of up to 1,000 μm were administered. During retraction of the sheath, the puncture channel was sealed with 2 ml of fibrinogen (Tissucol Duo; Baxter, Deerfield, IL, USA) to avoid bleeding or bile leakage. Fluoroscopy time and dose-area product were directly taken from the Philips Multi-diagnost Eleva (Philips Healthcare, Hamburg, Germany) console.

Volumetry

Gd-EOB-DTPA-enhanced magnetic resonance imaging (MRI) or contrast-enhanced CT before and approximately 4 weeks after PVE were used for volumetry. MRI volumetry was performed using thin-sliced hepatocyte-phase sequences. For CT volumetry, the venous phase was used.

Liver volume was measured by two clinical radiologists (4 and 16 years of experience) and two liver surgeons in consensus with surgeons using Visage Software 7.1 (Pro Medicus Limited, Richmond, Australia) manually delineating both the right liver lobe, including segments 4a and 4b, and the FRL (generally segments 2 and 3) according to the planned resection line respecting anatomical landmarks.

Body surface area (BSA) was calculated according to Mosteller’s formula. Estimated TLV was calculated from the patient’s BSA using the formula $TLV [cm^3] = -794.41 + 1,267.28 \times BSA [m^2]$ [21].

Anatomic Classification

Portal vein anatomy was classified using direct portography and preoperative cross-sectional images by two radiologists in consensus. The anatomic classification according to Couinaud was modified slightly [22–24]. Normal anatomy with right and left PV and division of right PV in right anterior segment and posterior segment was classified as type I. The other anatomic types are detailed in Fig. 1.

Statistical Analysis

Statistical analysis was performed by PASW Statistics 21 software (IBM, Armonk, NY, USA). To evaluate differences between groups, Student’s *t* test, Mann–Whitney *U*-test, Chi square test, or Fisher’s exact test was used according to the type of variable. ANOVA was used to evaluate differences in the anatomic groups. A *p*-value of <0.05 was considered

statistically significant. All quantitative data are expressed as mean ± standard deviation, unless otherwise indicated.

Results

Patient Characteristics

From July 2011 to December 2012, a total of 75 patients were included in our study. The PVE technique was changed from PO to additional CP/C embolization in March 2012. Therefore, 40 patients had PO embolization and 35 additional CP/C embolization (Fig. 2). Age, sex, and tumor entities did not differ significantly between the two groups (Table 1).

PV Embolization

The overall technical success rate was 100 %. Most punctures were ultrasound guided (88 % of PO group and 91 % of CP/C group). Fluoroscopy time was significantly higher in the CP/C group at 16.9 ± 6.0 min versus 14.8 ± 8.7 min (*p* = 0.015) in the PO group. The dose–area product in the CP/C group was higher at 261.9 ± 167.1 Gy * cm² versus 213.9 ± 166.7 Gy * cm² in the PO group, although the difference was not statistically significant (*p* = 0.082) (Table 1). In the CP/C group, a type I AVP with a diameter of 16 mm was used in the majority of cases (79 %). Coils with a diameter of 6–10 mm were used in 64 % of the cases. Details on the embolization materials used in both groups can be found in Tables 2 and 3.

Volumetry

Data on the imaging modalities used before PVE and before resection in the PO and CP/C groups are summarized in Table 1. The time from PVE to preoperative

I	II	III	IV	V	VI	VII
Right and left portal vein (RPV, LPV), division of RPV in RAS and RPS	Absent RPV, trifurcation in RAS, RPS and LPV	RAS (supplying seg. V & VIII) originates from LPV	RPS arises from main portal vein (MPV) before its bifurcation	RAS arises from main portal vein (MPV) before its bifurcation	Absent LPV, branch from RPV crosses umbilical fissure and supplies left liver	Absent RPV, RPS and RAS. Right liver is supplied by left portal branches

Fig. 1 Anatomical classification of portal vein anatomy in types I to VII [22–24]. *RPV* right portal vein, *RAS* portal vein of right anterior segment, *RPS* portal vein of right posterior segment, *LPV* left portal vein, *MPV* main portal vein

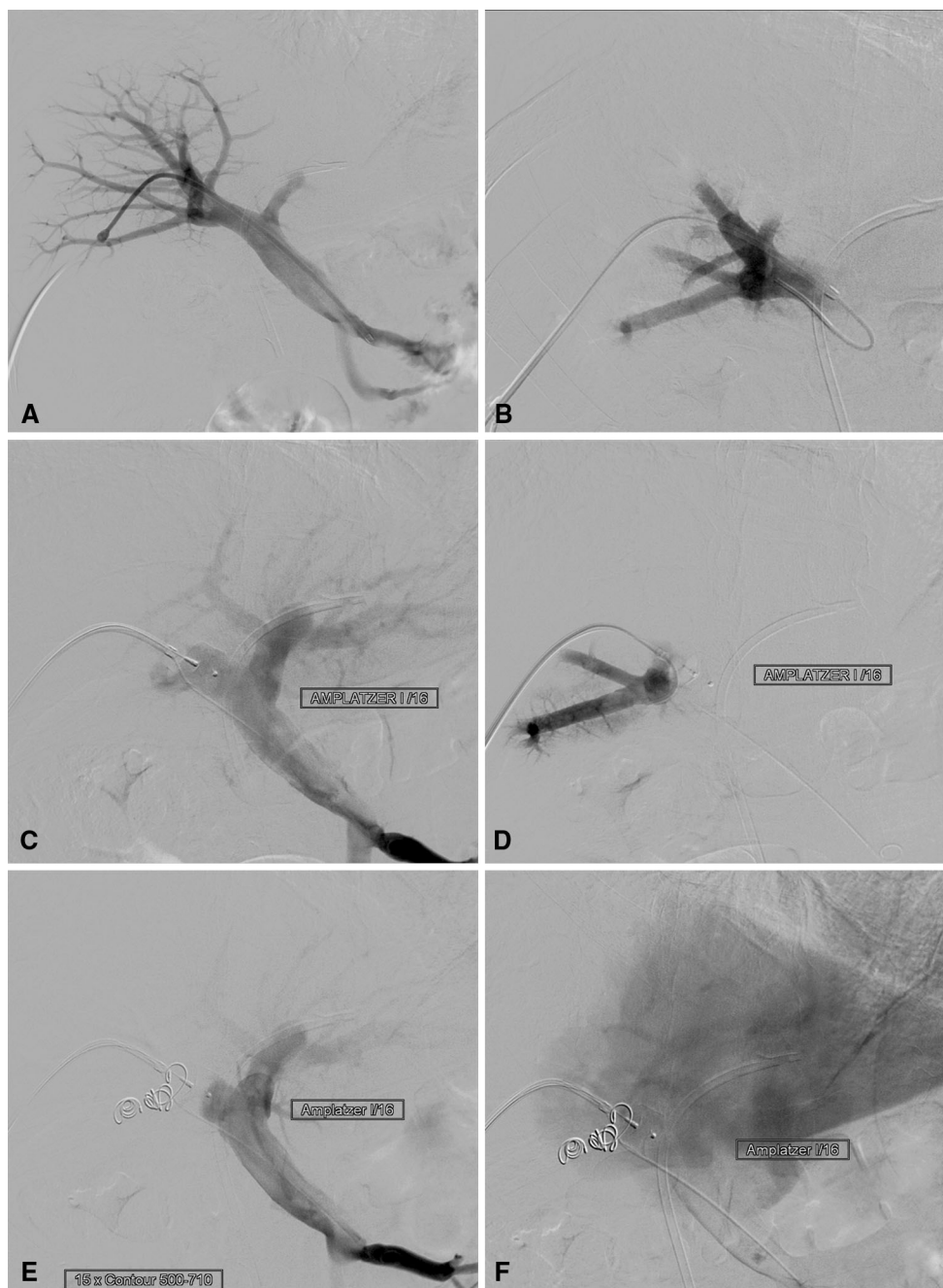


Fig. 2 A 66-year-old man with extrahepatic cholangiocarcinoma. Portography shows normal anatomy with right and left portal vein and division of RPV in right anterior and posterior segment (A). After particle embolization (B), a 16-mm type I AVP is placed to seal the

entry of the right main branch (C). Residual flow through AVP is embolized with additional coils (D). Final portography over a 3F pigtail catheter in the portal vein shows complete portal devascularization of right liver (E, F)

imaging was 29.1 ± 17.9 days in the PO group and 27.7 ± 6.9 in the CP/C group; the slight difference was not statistically significant ($p = 0.705$).

The ratio between the measured FRLV before embolization and the calculated TLV from BSA did not differ significantly in both groups ($p = 0.846$).

The average FRL volume of segments 2 and 3 before PVE was 328.9 ± 120.5 ml in the PO group and

332.7 ± 134.9 ml in the CP/C group ($p = 0.899$). The average FRL volume after PVE before resection was 419.2 ± 134.7 ml in the PO group and 491.7 ± 165.0 ml in the CP/C group, which differed statistically significantly ($p = 0.04$). The percentage gain in FRL volume in the CP/C group was significantly higher, with 53.3 ± 34.5 % compared to 30.1 ± 28.8 % in the PO group ($p = 0.003$, Fig. 3). The percentage of FRL volume of TLV before PVE was

Table 1 Group characteristics

Characteristic	Particles only	Particles and plug/coils	<i>p</i>
No. of subjects	40	35	
Sex			0.819
Male	23 (58 %)	19 (54 %)	
Female	17 (42 %)	16 (46 %)	
Age (y)	63.4 ± 11.5	62.8 ± 12.5	0.932
Tumor entity			0.826
ECC	23	21	
ICC	5	3	
CRC	5	9	
HCC	2	–	
FNH	–	1	
RCC	2	–	
Adenoma	–	1	
Melanoma	1	–	
GIST	1	–	
Unknown	1	–	
Tumor volume before PVE (ml)	71.1 ± 175.1	42 ± 68.3	0.359
Type of imaging before PVE			<0.01*
CT	24	5	
MRI	16	30	
Ratio of measured FRL before PVE from TLV estimated from BSA	0.212 ± 0.069	0.208 ± 0.078	0.846
Type of imaging before resection			<0.01*
CT	37	15	
MRI	3	20	
Time from PVE to preoperative imaging (days)	29.1 ± 17.9	27.7 ± 6.9	0.705
Type of puncture			0.622
US	35	32	
CT	4	3	
OP	1	–	
Dose–area product (Gy * cm ²)	213.9 ± 166.7	261.9 ± 167.1	0.082
Fluoroscopy time (min)	14.8 ± 8.7	16.9 ± 6.0	0.046*
Planned resection conducted	37 (93 %)	33 (94 %)	0.757

ECC extrahepatic cholangiocarcinoma, ICC intrahepatic cholangiocarcinoma, CRC colorectal cancer, HCC hepatocellular carcinoma, RCC renal cell carcinoma, GIST gastrointestinal stroma tumor, FNH focal nodular hyperplasia, TLV total liver volume, BSA body surface area, US ultrasound, CT computed tomography, OP intraoperative transileocolic

*Statistically significant

Table 2 Average material used in particles-only group

Characteristic	Value
No. of patients receiving contour particles	40 (100 %)
Average no. of Contour vials (all sizes) per patient	9.1 ± 3.7
Average no. of vials used by size	
Contour 250–355 µm	1 ± 1
Contour 355–500 µm	14 ± 2
Contour 500–710 µm	9 ± 4
Contour 710–1,000 µm	8 ± 8

18.8 ± 5.3 % for the PO group and 19.1 ± 5.3 % for the CP/C group. The percentage of FRL volume of TLV before resection was 24.7 ± 6.7 % for the PO group and 27.5 ± 5.7 % for the CP/C group. The percentages in both

groups before PVE and resection did not differ statistically significantly (*p* = 0.97 and *p* = 0.058), but the percentage gain in the ratio of FRL to TLV differed significantly (49.5 ± 24.2 % in the CP/C group versus 31.9 ± 26.6 % in the PO group, *p* = 0.004; Fig. 4).

PV Anatomy

In the PO group, 29 patients (73 %) had type I, 8 (20 %) type II, and 3 (8 %) type III anatomy. In the CP/C group, 27 patients (77 %) had type I, 4 (11 %) type II, 2 (6 %) type III, and 2 (6 %) type IV anatomy. There was no statistically significant difference in the anatomic types between the two groups (*p* > 0.05). No statistically significant difference in percentage gain in FRL volume was found according to anatomic type (*p* > 0.05).

Table 3 Average material used in the particles and plug/coil group

Characteristic	Value
No. of patients receiving contour particles	34 (97 %)
Average no. of Contour vials (all sizes) per patient	9.4 ± 4.3
Average no. of vials used by size	
Contour 250–355 µm	–
Contour 355–500 µm	3
Contour 500–710 µm	9 ± 4
Contour 710–1,000 µm	2 ± 1
Amplatzer plug used in <i>n</i> patients	28 (80 %)
10 mm type I	1
12 mm type I	1
14 mm type I	1
16 mm type I	22
12 mm type II	1
18 mm type II	2
No. of patients receiving coils	22 (64 %)
6–10 mm	5.8 ± 3.9

Furthermore, no statistically significant differences in fluoroscopy time and dose–area product were found ($p > 0.05$, Table 4).

Complications and Adverse Events

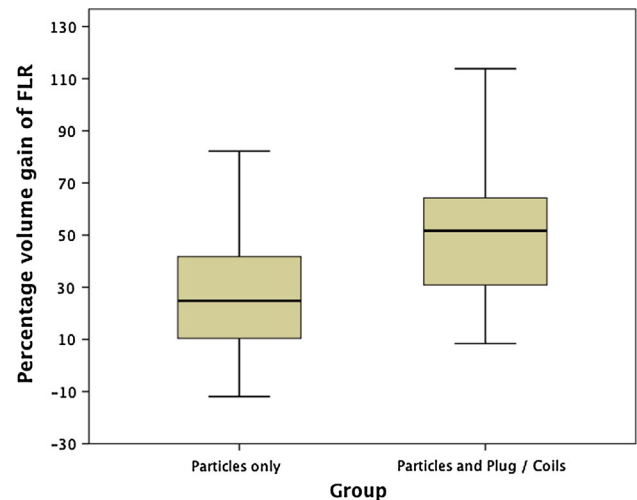
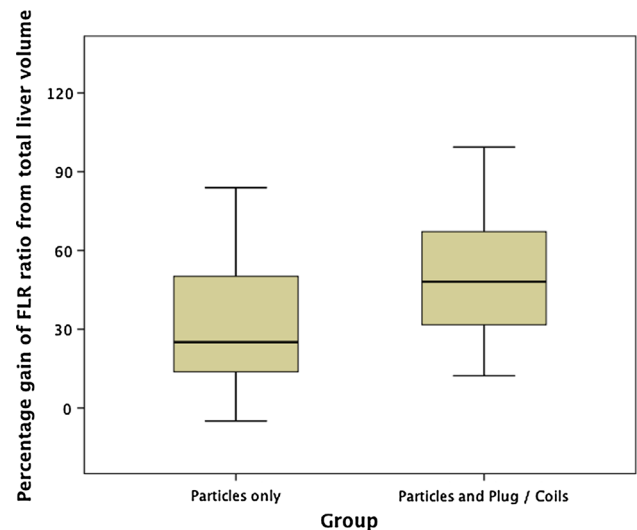
Four cases of extrahepatic biloma after PVE occurred, 1 (2.5 %) in the PO group and 3 (8.6 %) in the CP/C group, $p = 0.334$). All were treated with CT-guided percutaneous drainage and did not prohibit the planned resection. Overall, no complications precluding extended hemihepatectomy or PVE-associated deaths occurred.

Surgery

Planned major hepatectomy was conducted in 37 patients (93 %) in the PO group and 33 patients (94 %) in the CP/C group. Reasons for not performing surgery were disease progression in 2 patients and peritoneal carcinomatosis in 1 patient of the PO group and disease progression in 2 patients of the CP/C group. Disease progression in the left liver lobe was not the limiting factor.

Table 4 Types of portal vein anatomy and corresponding fluoroscopy time, dose–area product, and percentage volume gain

Characteristic	Particles-only group			Particles and plug/coil group			
	Type I	Type II	Type III	Type I	Type II	Type III	Type IV
<i>n</i> (%)	29 (73 %)	8 (20 %)	3 (8 %)	27 (77 %)	4 (11 %)	2 (6 %)	2 (6 %)
Fluoroscopy time (min)	13.8 ± 9.9	13.7 ± 6.7	11.9 ± 10.4	15.9 ± 6.1	18.4 ± 2.1	18.4 ± 6.9	25.9 ± 0.3
DAP (Gy·cm ²)	175.3 ± 151.1	198.1 ± 97.4	415.1 ± 363.6	247.3 ± 177.9	315.9 ± 148.2	270.9 ± 11.7	343.5 ± 174.7
Percentage volume gain	38.7 ± 29.1	13.0 ± 15.5	3.7 ± 16.8	50.9 ± 36.9	50.6 ± 20.0	84.1 ± 20.5	60.6 ± 32.2

**Fig. 3** Percentage volume gain of FRL in particles only and particles with additional plug and/or coil embolization**Fig. 4** Percentage gain of FRL ratio from TLV in particles only and particles with additional plug and/or coil embolization

Discussion

Today, PVE is the gold standard for inducing hepatic hypertrophy and is considered a reliable and efficient

technique [14–16, 19, 22]. Careful patient selection, close collaboration between surgeons and radiologists, individual functional assessment, and better surgical techniques have reduced postoperative mortality of major hepatectomy or hilar en-bloc resection to 2–9 % and have essentially eliminated hepatic insufficiency [4, 10, 25].

Our study has shown that right PVE with particles alone as well as particles and additional CP/C embolization are safe and lead to adequate hypertrophy of the left liver lobe, while the effect of an additional plug and/or coil embolization leads to a significantly higher hypertrophy of the FRL compared to PO embolization. The search for the supreme embolization material combining maximum hypertrophy with minimal adverse events while being effortless to handle is ongoing, and to our knowledge, no direct comparative studies exist.

Van Lienden et al. [15] published a comprehensive review, which—among other aspects—compared the FRL volume increase achieved with different embolic agents, of which NBCA had the most powerful effect. Although the follow-up interval may vary, seven studies including a total of 424 patients reported results on NBCA embolization; all data pooled showed an average percentage FRL volume increase of 49.9 %. We achieved a comparable average percentage FRL volume increase of 53.3 % in our patients. Some studies report an average percentage FRL volume increase of up to 74 %, which may be significantly higher than our results [26]. There are, however, two potential disadvantages of NBCA as an embolic agent for PVE. First, NBCA is more difficult to administer because it bears the risk of nontarget embolization, especially in patients with reduced hepatopetal portal flow. Second, it generates a peribiliary fibrosis, which may render hemihepatectomy more difficult [27, 28]. The advantage of NBCA is that material costs are significantly lower compared to particle or particle and plug/coil embolization.

Few clinical studies or case series exist that investigate the use of AVP combined with NBCA or PVA particles as a closure device for PVE; they report average percentage FRL volume increases of 27–68.9 % [20, 29–32]. Several cases of recanalized PV branches have been reported after PVE with particles alone [33, 34]; thus, the combination with AVP and large coils to prevent recanalization is compelling, and although we did not specifically investigate visible recanalization of major portal branches on follow-up imaging, our results show a significantly higher hypertrophy rate, which we explain by the combination of peripheral and central PV occlusion and therefore a minimum of reperfusion. Central plug/coil embolization enables precise release and possible repositioning, thereby minimizing the risk of nontarget embolization. By using AVP, the use of stainless steel coils—which result in significant artefacts on follow-up CT or MRI—can be decreased.

Embolization with an additional plug and/or coils had a higher incidence of biloma after PVE (three in the CP/C group and one in the PO group). This can be explained by the larger sheath (7–8F) that is required to deliver the AVP. Biloma, however, did not interfere with the planned surgical resection and could be treated by CT-guided drainage in all cases.

Our study has several limitations. First, the study design was retrospective; a prospective randomized trial would have better validity. Second, the imaging modalities before PVE and resection differed between MRI and CT and were not the same in all patients. CT and MRI measurements give slightly different, but not significantly different, volumes after manual volumetry, mainly because of breathing and partial volume effects [35, 36]. Finally, because selective embolization of segment IV branches was not performed and this segment is supplied by branches from either the left or right PV or from both, the distribution regarding the actual embolization of segment IV in the two groups may be different.

With increasing indications for PVE, further studies are needed to compare the competing embolic agents NBCA with PVA plus plug/coil embolization regarding the hypertrophy rate and the safety profile in a prospective and randomized setting.

A number of alternative methods to generate FRL volume gain should be mentioned. First, there is the possibility of hepatic artery embolization, which has, however, been shown to be less effective than PVE [12]. Another alternative is intraoperative PV ligation, which also seems to be less effective than PVE and can complicate the definitive resection [37]. In-situ splitting with PV ligation represents an alternate method, but one with a significantly higher mortality and morbidity rate, which has yet to be explored further [38].

In conclusion, right PVE with additional CP/C embolization leads to a significantly higher gain in FRL volume than embolization with particles alone.

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

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