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Original Article

Preoperative portal vein or portal and hepatic vein embolization: DRAGON collaborative group analysis

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Abstract

Background: The extent of liver resection for tumours is limited by the expected functional reserve of the future liver remnant (FRL), so hypertrophy may be induced by portal vein embolization (PVE), taking 6 weeks or longer for growth. This study assessed the hypothesis that simultaneous embolization of portal and hepatic veins (PVE/HVE) accelerates hypertrophy and improves resectability.

Methods: All centres of the international DRAGON trials study collaborative were asked to provide data on patients who had PVE/HVE or PVE on 2016–2019 (more than 5 PVE/HVE procedures was a requirement). Liver volumetry was performed using OsiriX MD software. Multivariable analysis was performed for the endpoints of resectability rate, FLR hypertrophy and major complications using receiver operating characteristic (ROC) statistics, regression, and Kaplan–Meier analysis.

Results: In total, 39 patients had undergone PVE/HVE and 160 had PVE alone. The PVE/HVE group had better hypertrophy than the PVE group (59 *versus* 48 per cent respectively; $P = 0.020$) and resectability (90 *versus* 68 per cent; $P = 0.007$). Major complications (26 *versus* 34 per cent; $P = 0.550$) and 90-day mortality (3 versus 16 per cent respectively, $P = 0.065$) were comparable. Multivariable analysis confirmed that these effects were independent of confounders.

Conclusion: PVE/HVE achieved better FLR hypertrophy and resectability than PVE in this collaborative experience.

Introduction

Portal vein embolization (PVE) and ligation (PVL) are used to induce growth of what would be a small future liver remnant (FLR) after resection for tumour(s)[1,2]. A systematic review[3] showed that the volume of the FLR increases by over one-third within a mean of 37 days following PVE yet as many as 40 per cent of patients with colorectal liver metastases (CRLM) who undergo PVE or PVL (in the context of two-stage hepatectomy) fail to achieve resection[4]. Insufficient FLR growth also remains a common problem in cholangiocarcinoma and hepatocellular carcinoma[3].

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) was introduced to improve outcomes of small FLR surgery[5]. Abrogation of the formation of portal vein collaterals between parts with and without portal flow accelerate regeneration by optimizing flow and minimizing hepatotrophic factor washout from the growing FLR[6]. Animal experiments have shown that portal vein collateral formation can be blocked by ipsilateral hepatic vein embolization (HVE) after PVL[7]. This simultaneous occlusion of both inflow and outflow, is feasible in humans[8] and can be designated "PVE/HVE". Indeed, the middle hepatic vein and related veins can also be embolized for an

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extended procedure[9–11]. PVE/HVE has been adopted by some centres because it may be more effective than PVE alone, owing to a perceived higher hypertrophy rate, and appears safer than ALPPS[12–16]. This multicentre Dragon collaborative study compared PVE/HVE with PVE alone.

Methods

The study was designed as a multicentre retrospective study. Centres had to be actively participating in the currently ongoing prospective one-arm DRAGON 1 study on the safety and feasibility of PVE/HVE for patients with CRLM only (www.dragontrial.com). Centres had to have performed more than five PVE/HVE procedures between January 2016 and December 2019. All centres were asked to submit anonymized data to a central data repository. Patients with all tumour types were included to reflect the clinical experience of participating centres, but an analysis of the colorectal subgroup was performed as well. A clinical risk score was calculated for patients with CLRM based on the Fong score[17]. Data are reported following the STROBE reporting guidelines for cohort studies[18].

Participants

Participating centres collected a comprehensive data set of all patients who had undergone either PVE/HVE or PVE. Data collection was conducted through the assessment of multidisciplinary tumour board records, planning logs, operating logs and embolization records by the individual centres. Collection of follow-up data ended in April 2020.

Variables

The primary endpoint of the study was feasibility of resection. The decision to resect was not defined homogeneously among centres, but all agreed with the common practice to resect once 30 per cent FLR had been reached. Not every centre used standardized FLR (sFLR) in their methodology. Secondary variables of interest were volume increase and clinical outcome.

Volume increase was assessed as absolute and relative volumes of the sFLR before and after the intervention. Relative volumes were described as sFLR calculated from standardized total liver volumes (TLVs), which were based on bodyweight (TLV = 18.51 × bodyweight (kg) + 191.8)[19]. Liver : bodyweight ratio was also used to assess the FLR[20]. The change in volumes was expressed by the metric percentage hypertrophy (%hypertrophy), degree of hypertrophy (DH), time between intervention and first imaging after intervention, time between intervention and resection, and kinetic growth rate (KGR). %Hypertrophy is the volume of the FLR before intervention (FLR1) divided by the volume of the FLR after intervention (FLR2). DH is the difference between sFLR2 and sFLR1 (DH = sFLR2 − sFLR1)[21]. KGR is DH divided by the time elapsed in weeks between the intervention and the first volume assessment after intervention[22].

Quantitative metrics of the intervention and surgical resection included duration, techniques, material used, blood loss, and length of hospital stay. Outcome parameters included R0 resection by histology, complications according to the Dindo–Clavien classification (complications of grade IIIA and above were defined as major complications)[23], posthepatectomy liver failure (PHLF) according to the International Study Group of Liver Surgery[24], 90-day mortality, recurrence and survival.

Data sources and management

Demographic data were retrieved from prospectively maintained databases, electronic health records, and clinical source documents. Liver volume was assessed by CT and MRI using OsiriX MD version 11.0.2 (Pixmeo SARL, Geneva, Switzerland). Tumour volume was subtracted from the FLR in cases the FLR was not free of tumour. Complications were assessed by comparison of prospectively maintained databases with source files such as discharge summaries and intervention logs.

Bias

Data reporting bias was reduced by systematic comparison with source files in electronic health records, pathology reports, tumour board records, and procedure and operative reports. Follow-up data were collected from prospectively maintained databases by centres, and bias was reduced by additional direct calls to care providers and patients in the respective centres. The decision to perform PVE/HVE or PVE was based on volumetry and judgement by the respective clinicians, which may have introduced a selection bias into the experimental group that cannot be excluded. This bias was addressed by performing multivariable analyses on the endpoints of feasibility of resection, %hypertrophy, and major complications. Patients with CRLM are reported separately because they comprise the largest subgroup and are of specific interest for the prospective DRAGON trials, which will limit enrolment to CRLM.

Study size

Study size was determined by all consecutive patients in 2016–2019, considering that PVE/HVE emerged as a new method in 2016. Effect sizes were used to perform the sample size calculation for the future RCT comparing PVE/HVE *versus* PVE (DRAGON 2).

Statistical analysis

All data in descriptive statistics were given as proportions for categorical variables and as mean(s.d.) (normal distribution) or median (i.q.r.) (non-normally distributed) values for continuous variables. For comparisons of groups, the *t* test and Mann–Whitney *U* test were used for normally and non-normally distributed variables respectively. Differences between categorical variables were assessed via Fisher's exact test. A two-tailed *P* value below 0.050 was considered significant. Multivariable analysis was performed using stepwise regression. Continuous variables were categorized for each endpoint separately using a receiver operating characteristic (ROC) analysis and the Youden Index as the cutoff. Analyses and graphics were performed using JMP® 15.0 (SAS Institute, Cary, NC, USA) and GraphPad Prism® (GraphPad Software, La Jolla, CA, USA). The Kaplan–Meier method was used for survival, recurrence-free survival and median follow-up.

Analysis of anonymized patient data was approved by the Cantonal Ethics Commission, Zurich, Switzerland (approval number 2018-02037).

Results

Fig. 1 shows participating centres. Among 40 centres participating in the DRAGON 1 trial, 21 performed PVE/HVE between 2016 and 2019. Eleven centres had performed fewer than five cases. Cases from one centre were not included because staged PVE and HVE was performed with an interval of more than 24 h. A second

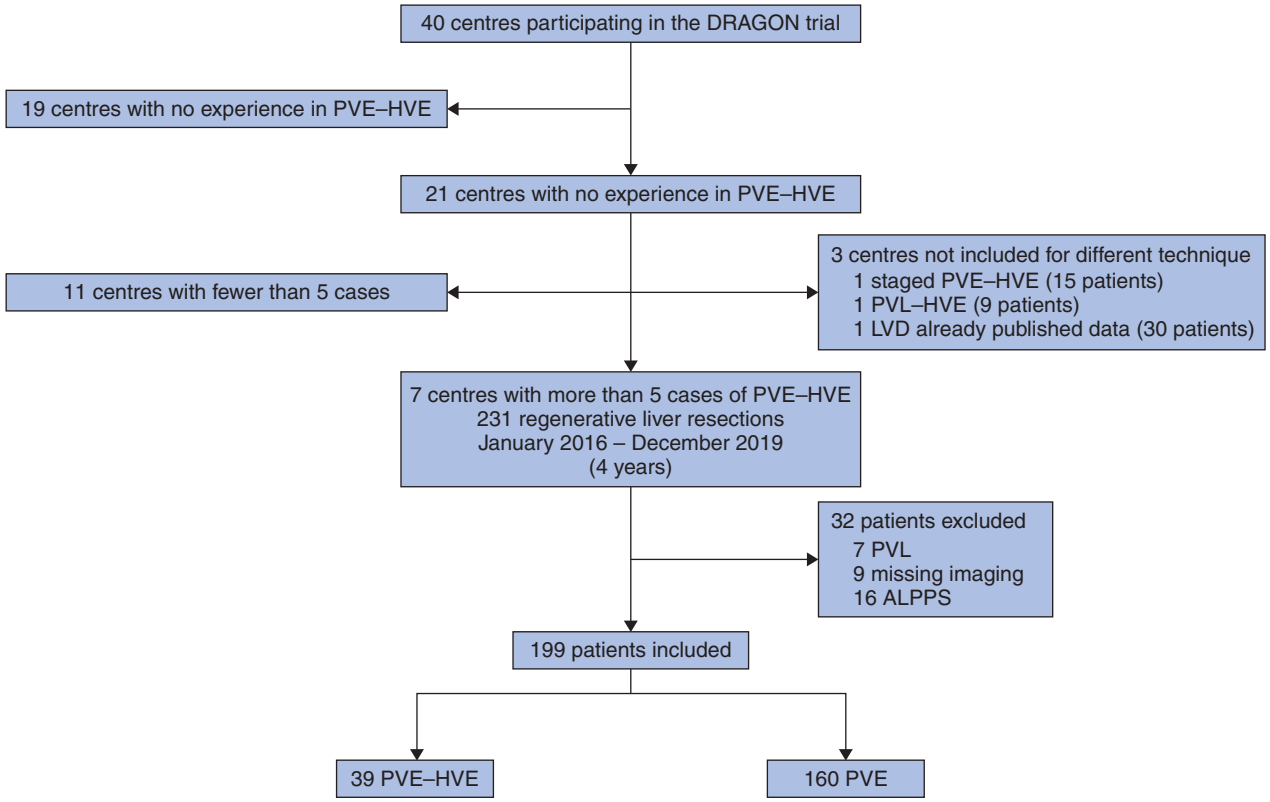

Fig. 1 Flow diagram of patients screened and included.

All 40 collaborating centres of the DRAGON trial were asked to contribute. Seven centres performed more than five simultaneous portal and hepatic vein embolization (PVE/HVE) procedures over 4 years, and 231 regenerative liver resections were included. PVL, portal vein ligation; LVD, liver venous deprivation technique (Montpellier method); ALPPS, associating liver partition and portal vein ligation for staged hepatectomy.

centre performed intraoperative PVL followed by HVE after a few days. A third centre had already reported their results and was not included to avoid double reporting[8]. In seven centres, 231 procedures were performed between January 2016 and December 2019. Among the analysed patients, those undergoing PVL (7 patients) and ALPPS (16) were excluded. Imaging was not available for nine patients. The analysis cohort ultimately consisted of 199 patients (39 PVE/HVE, 160 PVE).

Descriptive data

Demographics are given in *Table 1*. Age ($P = 0.008$) and Charlson Co-morbidity Index ($P = 0.004$) differed between the two groups. The most common tumour type was CRLM. More patients in the PVE group had fibrosis and cirrhosis, and more patients in the PVE–HVE group had steatosis ($P = 0.021$).

Missing data

Blood loss could not be determined in four patients in the PVE group because it was not assessed routinely in one centre. Information on carcinoembryonic antigen level was not available for one patient.

Outcome data

Intervention data are summarized in *Table 2*. PVE was performed more frequently in the outpatient setting compared with PVE/HVE ($P = 0.008$). Embolization with *N*-butyl-cyanoacrylate (NBCA)/lipiodol was the dominant technique for the PVE component, in both groups. None of the participating centres performed additional segment IV embolization. All liver vein embolizations were performed with Amplatzer™ vascular plugs (St-Jude Medical, Plymouth, MN), no additional liquid embolization was used by any centre.

The overall complication rate was 15 and 15.6 per cent after PVE/HVE and PVE respectively, the majority being pain and fever (postembolization syndrome). Major complications occurred in four patients; all were all 90-day deaths. One patient in the PVE/HVE group died from septic shock due to infected tumour necrosis after the intervention. Three patients undergoing PVE died: one from septic shock with cholangitis; one developed gastric bleeding, haemorrhagic shock, treatment with coagulation factors, and pulmonary embolism; and one patient died from an unrelated thrombosis of the basilar artery.

Resection data are summarized in *Table 3*. Feasibility of resection was 22 per cent higher after PVE/HVE compared with PVE ($P = 0.007$). Among patients who demonstrated insufficient liver growth after PVE, five had rescue HVE with an interval of several days between PVE and rescue HVE. Time from intervention to first liver volumetry was shorter for patients undergoing PVE/HVE (17 *versus* 24 days respectively; $P = 0.009$). FLR and sFLR volumes reached after hypertrophy did not differ, but the metric %hypertrophy was 11 per cent higher in the PVE/HVE group ($P = 0.020$) and the KGR was higher after PVE/HVE ($P < 0.001$). KGR did not differ between right HVE and right plus middle HVE (data not shown). Some 83 per cent of all resections performed in the PVE/HVE group were extended right hepatectomies, compared with 45.9 per cent in the PVE group. The rates of PHLF and 90-day mortality were 11 and 3 per cent respectively in the PVE–HVE group, compared with 24.8 and 15.6 per cent in the PVE group ($P = 0.145$ and $P = 0.065$ respectively). Ninety-day deaths after resection were caused by haemorrhagic shock in one patient in

Table 1 Demographics

	PVE–HVE ($n = 39$)	PVE ($n = 160$)	P†
Age (years)*	63 (52–67)	67 (58–73)	**0.008‡**
Sex ratio (F : M)	18 : 21	61 : 99	0.359
Charlson Co-morbidity Index*	6 (5–7)	7 (6–9)	0.004‡
BMI (kg/m²)*	24.4 (22.7–26.9)	25.2 (23–28.3)	0.307‡
Type of tumour			0.515
CRLM	19 (49)	85 (53.6)	
HCC	4 (10)	11 (6.9	
IHCC	4 (10)	22 (13.8)	
PHCC	5 (13)	25 (15.6)	
Gallbladder cancer	4 (10)	9 (5.6)	
Other	3 (8)	8 (5.0)	
Creatinine at baseline (μmol/l)*	71 (60.1–84)	74.2 (65.1–91.5)	0.174‡
Bilirubin at baseline (μmol/l)*	10.3 (5.6–13.5)	7.9 (5.1–11.7)	0.101‡
INR at baseline*	1.02 (0.95–1.10)	1.01 (0.96–1.06)	0.677‡
Liver status			0.021
Normal	20 (51)	88 (55.0)	
Fibrosis	1 (3)	22 (13.8)	
Steatosis	17 (44)	37 (23.1)	
Cirrhosis	1 (3)	13 (8.1)	
Diabetes	4 (10)	28 (17.5)	0.270
Chemotherapy	19 (49)	77 (48.1)	0.758
FOLFOX/XELOX	14 of 19 (74)	50 of 77 (65)	
FOLFIRI/XELIRI	2 of 19 (11)	13 of 77 (17)	
FOLFORINOX	2 of 19 (11)	10 of 77 (13)	
Other	1 of 19 (5)	4 of 77 (5)	
Biological agent	13 of 19 (68)	60 of 77 (78)	0.766
Bevacizumab	4 of 13 (31)	39 of 60 (65)	0.040
Cetuximab/panitumumab	9 of 13 (69)	21 of 60 (35)	

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). PVE/HVE, simultaneous portal vein embolization (PVE) and hepatic vein embolization; CRLM, colorectal liver metastases; HCC, hepatocellular carcinoma; IHCC, intrahepatic cholangiocarcinoma; PHCC, perihilar cholangiocarcinoma; INR, international normalized ratio. †Fisher's exact test, except ‡Mann–Whitney *U* test.

the PVE–HVE group, and by sepsis with multiple organ failure (11 patients), postoperative bleeding (5) and stroke (1) in the PVE group. Median time to follow-up was 165 and 201 days after PVE–HVE and PVE respectively ($P = 0.039$).

Multivariable analysis for resectability, percentage hypertrophy, and major complications

Odds ratios for resectability and their precision (c.i.) are given in *Table S1*. Among nine co-variables with potential clinical relevance for resectability, only tumour type and intervention remained significant in the multivariable analysis.

Among 12 co-variables with potential relevance for more than 50 per cent hypertrophy, only size of the FLR remained significant in the multivariable analysis (*Table S2*).

Among 16 co-variables with potential relevance for major complications BMI, diseased parenchyma, time from radiology intervention to resection greater than 99 days, or abnormal international normalized ratio before resection, duration of surgery longer than 7 h, blood transfusion of more than 2 units, and intervention PVE/HVE *versus* PVE remained significant in the multivariable analysis (*Table S3*).

Subgroup analysis of colorectal liver metastases

The subgroup analysis of CRLM is shown in *Table S4*. As in the overall cohort, there was a difference in time to first imaging between PVE/HVE and PVE, %hypertrophy, DH and KGR. Duration of surgery was also different.

Sensitivity analysis of patients with comparable time to first imaging

As patients in the PVE/HVE group underwent volumetry significantly earlier and differed in age, Charlson Co-morbidity Index, liver status, and the administration of bevacizumab, a sensitivity analysis was performed. This was done by assigning a 1 : 1 match, based on age, Charlson Index, cirrhosis, presence of diabetes, whether patients received bevacizumab, and the closest times to first imaging for each pair of patients. In addition, only PVEs were included that used NBCA/lipiodol for PVE/HVE and PVE, and only PVE/HVE procedures were considered that used Amplatzer™ vascular plugs for HVE (35 patients). The volume kinetics of all 199 patients expressed in sFLR over time in weeks are shown in *Fig. 2a*, and the results of volume kinetics of matched patients are shown in *Fig. 2b*. The characteristics of the 35 matched patients in each group are given in *Table S5*.

Follow-up of all patients and survival of patients with colorectal liver metastases

Time to follow-up is shown in *Fig. S1a*. As the Kaplan–Meier statistic showed a significant difference in time to follow-up between the two groups, with shorter follow-up for PVE–HVE, a difference in the distribution of enrolment in the time period 2016–2019 between the two groups was clear, and therefore an era bias cannot be excluded completely. Overall and recurrence-free survival were analysed only for patients with CRLM (due to comparable biology of disease) and are shown in *Fig. S1b and S1c* respectively. There was no difference between groups.

Table 2 Intervention

	PVE–HVE ($n = 39$)	PVE ($n = 160$)	P†
Two-stage hepatectomy	7 (18)	48 (30.0)	0.134
Liver volume before intervention*			
FLR1 (ml)	281 (234–352.1)	294 (233–389.7)	0.829‡
sFLR1 (%)	18 (16–23)	18.5 (15–25)	0.804‡
LBWR1 (ml/kg bodyweight)	0.38 (0.33–0.48)	0.39 (0.31–0.53)	0.734‡
Technical details			
Outpatient	22 (56)	125 (78.1)	0.008
PVE			
Portal vein			0.784
Right	38 (97)	157 (98.1)	
Left	1 (3)	3 (1.9)	
Occlusion technique			0.002
NBCA/lipiodol	39 (100)	134 (83.8)	
NBCA/lipiodol + Amplatzer™	0 (0)	2 (1.3	
Microparticles	0 (0)	9 (5.6)	
Microparticles+ NBCA/lipiodol	0 (0)	15 (9.4)	
Approach			
Ipsilateral	38 (97)	154 (96.3)	0.721
Contralateral	1 (3)	6 (3.8)	
HVE			
Right HVE	27 (69)		
Right + middle HVE	11 (28)		
Left HVE	0 (0)		
Left + middle HVE	1 (3)		
Occlusion technique			
Amplatzer™	35 (90)		
Amplatzer™ + NBCA/lipiodol (LVD)	0 (0)		
Amplatzer™ + coils	4 (10)		
Approach			
Transjugular	15 (38)		
Transhepatic	24 (62)		
Complications			
Overall	6 (15)	25 (15.6)	0.895
Fever/pain	5 (13)	22 (13.8)	0.879
90-day mortality	1 (3)	3 (1.9)	0.783

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). PVE/HVE: simultaneous portal vein embolization (PVE) and hepatic vein embolization (HVE); FLR, future liver remnant; sFLR, standardized FLR; LBWR, liver : bodyweight ratio; NBCA, *N*-butyl-cyanoacrylate; LVD, liver venous deprivation technique (Montpellier method). †Fisher's exact test, except ‡Mann–Whitney *U* test.

Discussion

PVE/HVE results in a higher resectability rate for all types of liver tumour, induces a higher percentage of liver hypertrophy resulting in a larger FLR, and has a safety profile similar to that of PVE. The analysis has shown that smaller sFLRs grow faster and confirmed that the advantage of PVE/HVE over PVE with regard to resectability and complication rates is robust. Only for the endpoint of volume increase was the starting volume of the FLR more important than group allocation. The mortality rate for resection after PVE was high, but confirms the concerns of high mortality after two-stage resections in other reports[4,25].

The clinical importance of a higher resectability rate of CRLM was demonstrated recently in the LIGRO trial[4]. Patients with primarily unresectable CRLM underwent either ALPPS or PVE or PVL, and the resection rate after ALPSS was superior to that after conventional two-stage liver resection. A later follow-up[26] demonstrated that the increased resectability induced by ALPPS translated into better medium-term survival. Despite this, ALPPS has faced limited acceptance owing to a problematic safety profile[4,27–29]. Rapid hypertrophy, however, does not depend on ALPPS, but can also be induced by simultaneous portal and hepatic vein occlusion. The present study demonstrated that PVE/HVE provides clinicians with tool to increase resectability over PVE, which had not been shown previously[30]. PVE/HVE provides a safety profile comparable to that of PVE and superior to that of ALPPS, although postembolization syndrome seems to be underreported here[30].

This study has several limitations. Owing to its retrospective design and lack of funding for independent monitoring, a reporting bias cannot be excluded. There may have been selection bias for easier cases to be treated with PVE/HVE. Age and comorbidity appeared lower in the PVE/HVE group, and PVE/HVE was used less commonly in the context of a two-stage hepatectomy. The subgroup analysis of CRLM showed no statistically relevant difference in resectability rate, with a smaller difference than for the entire group, which may be due to the limited number. In addition, the resectability rate for the PVE control group in the CRLM subgroup was quite high compared with that in the published literature. However, such a bias based on clinical risk could not be detected when the Fong clinical risk score or its components were examined. Imaging was performed earlier for PVE/HVE than for PVE, resulting in a smaller denominator for kinetic growth. Additionally, the exclusive use of glue for PVE in the PVE/HVE cohort may have resulted in a bias, as patients in the PVE group underwent embolization with microparticles whereas the others had microparticles and glue. A sensitivity analysis confirmed increased volume growth for PVE/HVE, even in the matched cohorts.

Acceleration of liver growth by PVE/HVE compared with conventional means was first reported in a case series of seven

Table 3 Resection

	PVE–HVE ($n = 39$)	PVE ($n = 160$)	$P^{\dagger}$
Feasibility of resection	35 (90)	109 (68.1)	0.007
Failure of resection	4 (10)	51 (31.9)	
Progression of disease	2	31	
Insufficient liver growth	1	17	
Postinterventional complications	1	3	
Liver volume after intervention			
Time from intervention to first volumetry (days)*	17 (13–32)	24 (19–37)	0.009‡
FLR (ml)*	470 (381.9–598.4)	442 (342–562.5)	0.227‡
sFLR (%)*	31 (24–39)	28 (21–37)	0.102‡
LBWR (ml/kg bodyweight)*	0.66 (0.52–0.85)	0.6 (0.45–0.77)	0.105‡
FLR increase (ml/day)*	7 (5–18)	6 (2–9)	0.002‡
%Hypertrophy*	59 (45–79)	48 (24–69)	0.020‡
%Hypertrophy/week*	21 (11–33)	13 (6–20)	< 0.001‡
Degree of hypertropy (%) *	10 (8–14)	9 (5–13)	0.017‡
Kinetic growth rate (sFLR/week)*	3.5 (2.2–7.1)	2.5 (1.1–3.8)	< 0.001‡
Kinetic growth rate ≥ 2.0 (sFLR/week)	30 (77)	92 (57.5)	0.026
Resection	$n = 35$	$n = 109$	
Time from intervention to resection (days)*	37 (21–52)	41 (28–61)	0.132‡
Type of resection			< 0.001
Right hepatectomy	5 (14)	55 (50.5)	
Extended right hepatectomy	29 (83)	50 (45.9)	
Left hepatectomy	0 (0)	2 (1,8)	
Extended left hepatectomy	1 (3)	2 (1.8)	
Laparoscopic resection	0 (0)	12 (11.0)	0.051
Duration of surgery (min)*	321 (209.5–442.5)	385 (311–434.5)	0.031‡
Blood loss (ml)*	800 (500–1450)	650 (400–1500)	0.468‡
Hospital stay (days)*	9 (6–18)	11(8–20)	0.100‡
Bilirubin at POD 5 (μmol/l)*	20.9 (13.8–37.2)	17.4 (11.3–28.1)	0.131‡
INR at POD 5*	1.12 (1.06–1.22)	1.25 (1.15–1.43)	< 0.001‡
Creatinine at POD 2 (μmol/l)*	67.6 (52.8–76.9)	76 (60.1–105)	0.029‡
PHLF per ISGLS criteria	4 (11)	27 (24.8)	0.145
R0 resection	28 (80)	88 (80.7)	0.472
Complications	$n = 35$	$n = 109$	
Overall	17 (49)	69 (63.3)	0.299
Major (Dindo–Clavien grade > IIIA)	9 (26)	37 (33.9)	0.546
90-day mortality after resection	1 (3)	17 (15.6)	0.065

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). PVE–HVE, simultaneous portal vein embolization (PVE) and hepatic vein embolization; FLR, future liver remnant; sFLR, standardized FLR; LBWR, liver : bodyweight ratio; %hypertrophy, increase in FLR volume expressed as a percentage; INR, international normalized ratio; PHLF, posthepatectomy liver failure; ISGLS, International Study Group of Liver Surgery. †Fisher's exact test, except ‡Mann–Whitney *U* test.

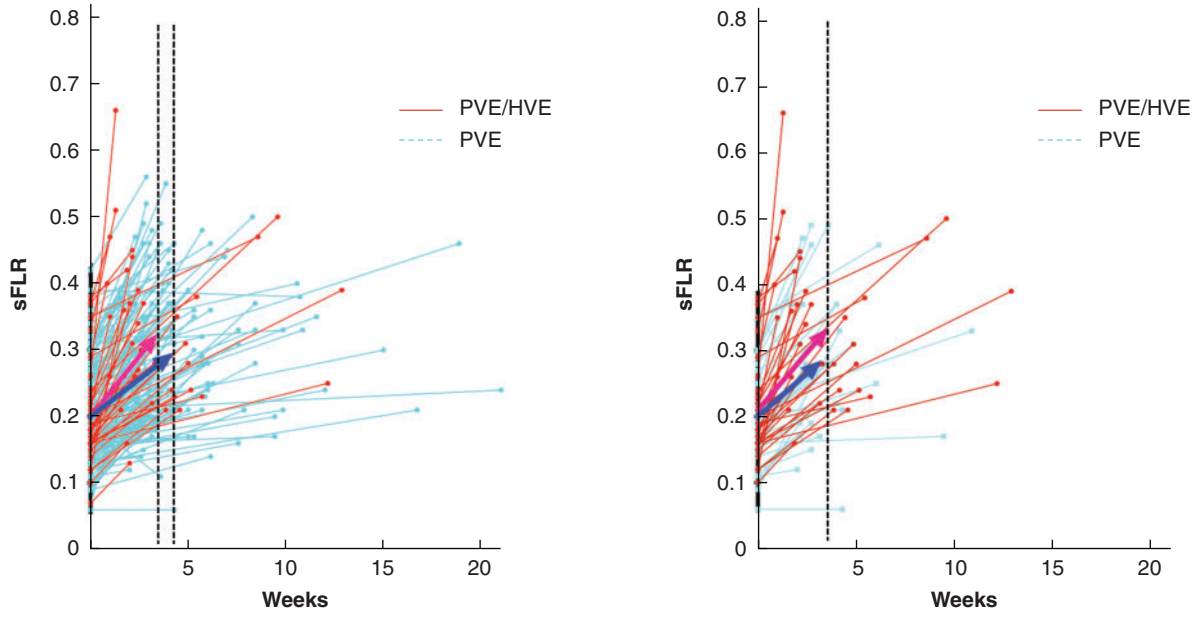

Fig. 2 Kinetic growth rate

Volume increase of standardized future liver remnant (sFLR) simultaneous portal and hepatic vein embolization (PVE/HVE) *versus* portal vein embolization (PVE) for **a** all patients and **b** matched subgroups. The coloured arrows show median liver growth for PVE–HVE (red) and PVE (blue).

patients in 2016[8], which used liquid embolization additional to hepatic vein occlusion and called the procedure "liver venous deprivation" (LVD). Subsequently, in an extended series of 10 patients undergoing extended LVD (eLVD), a parallel growth of volume and function was demonstrated by mebrofenin scintigraphy[9]. This is important, because there was evidence of reduced function compared with volume growth in ALPPS, potentially leading to worse outcomes[10,31]. Unfortunately, in the present study only one centre obtained mebrofenin scintigraphy after PVE/HVE. Therefore, functional changes could not be evaluated here.

Three other Studies comapring PVE/HVE and PVE have ben published[12,13,16]. All are signle centre retrospective experiences. They differ from this study in that they did not show a difference in resectability[12,13,16]. In one study, the compared groups had different starting volumes[16] or included patients with quite large starting volumes (f.e. 547cc or 25% FLR for PVE/HVE and 523cc or 24% for PVE)[12]. High starting volumes[2,13] also explain the lower rate of hypertrophy demonstrated[12], since this study shows that smaller liver volumes grow faster, which confirms previous studies[32]. The studies are also technically heterogenous, some used venous liquid of hepatic veins additionally to Amplatzer™ vascular plugs, the hellmark of the "LVD" technique, without calling the technique "LVD"[16], and some call their technique "LVD" without using liquid embolization[12].

The DRAGON collaborative decided to forego additional venous liquid embolization in the ongoing trial (NCT04272931) based on a DELPHI process due to the potential risk of systemic pulmonary glue embolization. One study has replaced the practice of PVE (2010-2016) entirely by PVE/HVE (2016-2018) and thereby induces an era bias[12]. Despite the observed advantage, the DRAGON collaborative does not support replacement of PVE by PVE/HVE without randomizd evidence from ongoing trials (DRAGON: NCT04272931, LVD France: NCT03995459).

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Supplementary material

Supplementary material is available at *BJS Open* online.

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