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Original Article

Liver regeneration after portal and hepatic vein embolization improves overall survival compared with portal vein embolization alone: mid-term survival analysis of the multicentre DRAGON 0 cohort

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Abstract

Background: The purpose of this study was to compare 3-year overall survival after simultaneous portal (PVE) and hepatic vein (HVE) embolization *versus* PVE alone in patients undergoing liver resection for primary and secondary cancers of the liver.

Methods: In this multicentre retrospective study, all DRAGON 0 centres provided 3-year follow-up data for all patients who had PVE/HVE or PVE, and were included in DRAGON 0 between 2016 and 2019. Kaplan–Meier analysis was undertaken to assess 3-year overall and recurrence/progression-free survival. Factors affecting survival were evaluated using univariable and multivariable Cox regression analyses.

Results: In total, 199 patients were included from 7 centres, of whom 39 underwent PVE/HVE and 160 PVE alone. Groups differed in median age ($P = 0.008$). As reported previously, PVE/HVE resulted in a significantly higher resection rate than PVE alone (92 *versus* 68%; $P = 0.007$). Three-year overall survival was significantly higher in the PVE/HVE group (median survival not reached after 36 months *versus* 20 months after PVE; $P = 0.004$). Univariable and multivariable analyses identified PVE/HVE as an independent predictor of survival (univariable HR 0.46, 95% c.i. 0.27 to 0.76; $P = 0.003$).

Conclusion: Overall survival after PVE/HVE is substantially longer than that after PVE alone in patients with primary and secondary liver tumours.

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Introduction

Partial resection of the liver is central to the oncological treatment strategy to extend overall survival associated with several liver cancers, including colorectal liver metastases (CRLMs), hepatocellular carcinoma, and cholangiocarcinoma. Favourable long-term outcomes are achieved when complete resection can be accomplished. Resectability, however, is limited by the capacity of the future liver remnant (FLR), so only 30% of patients with primary or secondary cancers to the liver qualify for resection[1,2].

FLR hypertrophy-inducing procedures help to overcome that limitation, and aim to improve volume and function of the FLR before major liver resection in patients with a small FLR at risk of posthepatectomy liver failure (PHLF). In general, to prevent PHLF, a FLR of 30% in patients without underlying liver disease (for example fibrosis or cirrhosis) is considered as a safe cut-off for major liver resections[3–5].

Portal vein embolization (PVE) is the current standard FLR hypertrophy-inducing procedure[6–8]. PVE-induced hypertrophy, however, is relatively slow and often results in a long wait to gain sufficient liver growth. As a result, approximately 30–40% of patients do not undergo resection, mainly owing to tumour progression while awaiting sufficient liver growth[9]. Rapid FLR growth may help to prevent this failure to progress to resection[10]. Moreover, studies[11] have shown that a high kinetic growth rate (KGR) yields low morbidity after partial hepatectomy.

FLR hypertrophy can be accelerated by the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure, in which portal vein collaterals are prevented by surgical transection (*in situ* split) of the liver parenchyma in addition to portal vein ligation[12]. Despite increased FLR hypertrophy resulting in an improved resection rate, ALPPS requires two operations, and is associated with a high morbidity and mortality rate mainly associated with PHLF[13,14]. Therefore, ALPPS is considered to be a high-risk alternative to PVE.

Contemporary oncological care is characterized by optimization of surgical care pathways, personalization of treatments, and a fast-growing use of percutaneous approaches to minimize the impact on the patient. Within that perspective, simultaneous embolization of the portal and hepatic veins (PVE/HVE) has been introduced. Multiple studies have shown that PVE/HVE induces rapid liver hypertrophy to a similar extent as observed in ALPPS, without the need for a highly invasive procedure and associated morbidity and mortality[15]. The technique, in which the hepatic outflow is occluded in addition to conventional PVE, was first described by Guiu *et al.*[16]. However, Guiu and colleagues additionally injected glue into the hepatic veins and described the procedure as liver venous deprivation (LVD). Many centres perform a simplified version of LVD, called PVE/HVE or 'double embolization', whereby one or two hepatic veins are occluded with vascular plugs only. The DRAGON collaborative, an international group of 70 major hepatopancreatobiliary centres set up to study PVE/HVE prospectively, decided in consensus to refrain from the additional application of glue to minimize the risk of migration of embolization material.

The recent retrospective observational DRAGON 0 study demonstrated a substantially increased resection rate, comparable to that of ALPPS, after PVE/HVE, with a safety profile similar to that of PVE alone[17]. These findings were confirmed in a meta-analysis of all published comparative studies comparing PVE/HVE *versus* PVE alone, and fit well in the contemporary development of minimization of the physical impact of oncological treatments[18,19]. It has not yet been determined whether this also translates into better oncological outcomes. Therefore, the aim of this study was to assess the 3-year overall survival and recurrence/progression-free survival of the retrospective DRAGON 0 cohort, currently the largest comparative series on PVE/HVE.

Methods

Ethical approval

The study was approved by the ethical review board azM/UM (approval number 2019-1375) and conducted in accordance with the Declaration of Helsinki of 1996.

Study design and settings

This study was designed as a multicentre retrospective cohort study in which seven centres of the DRAGON collaborative enrolled patients who had PVE or PVE/HVE between January 2016 and December 2019. The primary manuscript, assessing hypertrophy and resection rate, was published in 2021[17]. For the present study, all centres were additionally requested to provided 3-year follow-up data on all enrolled patients. In the event of insufficient liver growth following PVE, a cross-over to rescue HVE did not occur in any patient. Patients in whom surgical resection failed for any reason after embolization (either PVE or PVE/HVE) were included in the overall survival analysis and recurrence/progression-free survival analysis by intention to treat. Data are reported in accordance with the STROBE reporting guidelines for cohort studies[20].

Participants

All centres in the international DRAGON collaborative that undertook more than five PVE/HVE procedures between 2016 and 2019 provided patient, imaging, and follow-up data from local databases, multidisciplinary tumour board records, planning and operation logs, and embolization protocols. If follow-up data were missing, the centres' active surveillance programmes, patients and primary-care physicians were contacted.

Variables

The primary endpoint of this analysis was 3-year overall survival. Secondary variables of interest were 3-year recurrence/progression-free survival, volumetric data, and postoperative outcomes including 90-day mortality. Volumetric data for the liver were specified as standardized FLR (sFLR) based on Vauthey's formula ($18.51 \times \text{bodyweight} + 191.8$)[21]. Liver growth was provided as KGR, calculated as the difference between the sFLR before and after embolization divided by the time elapsed between the intervention and first volumetric assessment[11]. The surgical resection procedure was classified according to the Brisbane terminology (right hepatectomy: segments V–VIII; extended right hepatectomy: segments IV–VIII by indication including segment I; left hepatectomy: segments II–IV; extended left hepatectomy: segments II–IV + V and VIII)[22]. Postoperative complications and PHLF were assessed according to the Clavien–Dindo classification[23] and International Study Group of Liver Surgery (ISGLS) criteria[24] respectively. Tumour type and surgical resection status (R) were based on the final pathology reports of the individual hospitals.

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Subgroups

A subgroup analysis was undertaken for patients with CRLM because such patients represent the largest cohort in this study. Additionally, the 3-year oncological outcome was assessed using the 1 : 1 matched subgroup from the previous DRAGON 0 publication[17]. The 1 : 1 match was carried out in consideration of following parameters: age, Charlson index, cirrhosis, diabetes, whether the patient received bevacizumab, and interval from intervention to first volumetric assessment.

Sensitivity analysis for time bias

Owing to the retrospective nature of the study, selection bias could not be avoided. Likewise, an era bias could not be ruled out because of the increased performance of PVE/HVE in recent years. To check the era bias, a multivariable analysis was conducted corrected for year of embolization. The decision to resect was not based on a prospectively defined FLR volume cut-off; however, all participating centres accepted a FLR volume cut-off of 30% for normal livers and 40% for patients with underlying liver disease.

Statistical analysis

Categorical variables are presented as number of patients with percentage, and continuous variables as median (i.q.r.). To compare groups, Mann–Whitney *U* test was used for continuous data, and χ^2 test or Fisher's exact test for categorical variables. Kaplan–Meier analysis in combination with the log rank test was performed to analyse 3-year recurrence/progression-free and overall survival. If there was no evidence of survival status (deceased or still alive), the last date when the patient was seen was used as censoring date. A univariable Cox regression analysis was used to assess the group effect (PVE/HVE *versus* PVE alone). Based on available evidence, factors that might have an impact on survival were considered for the multivariable analysis using the all-in technique. Cox regression analysis was used for this analysis. Analyses were undertaken and graphics created using JMP® 15.0 (SAS Institute, Cary, NC, USA) and GraphPad® Prism (GraphPad Software, La Jolla, CA, USA). Two-sided $P \leq 0.050$ was considered statistically significant.

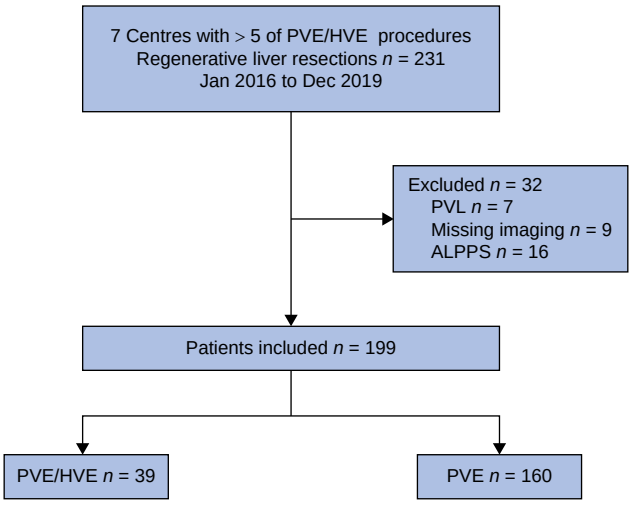


Fig. 1 Study flow chart

PVE, portal vein embolization; HVE, hepatic vein embolization; PVL portal vein ligation; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy.

Results

In 7 centres of the DRAGON collaborative that provided data for both the initial comparative series and this oncological follow-up analysis, 39 patients underwent PVE/HVE and 160 patients PVE alone (*Fig. 1*). There was no significant difference in demographics, except for patient age (*Table 1*). CRLM was the most common tumour type.

Updated follow-up data indicated that 92% of patients who underwent PVE/HVE had tumour resection. This was 2% higher than noted in the initial report as one patient was initially considered not to have undergone resection owing to insufficient liver growth in the primary study interval[17]. In the PVE group, the resection rate was still 68% ($P = 0.007$).

The KGR was significantly higher after PVE/HVE compared with PVE alone. More patients underwent extended liver resections after PVE/HVE, whereas operating times were longer in the PVE group (*Table 2*). There were no significant differences in postoperative complications (Clavien–Dindo), PHLF (ISGLS), and 90-day mortality between the two groups.

Table 1 Patient demographics

	PVE/HVE ($n = 39$)	PVE ($n = 160$)	P*
Age (years), median (i.q.r.)	63 (52–67)	67 (58–73)	0.008†
Sex			0.359
Female	18 (46)	61 (38)	
Male	21 (54)	99 (62)	
BMI (kg/m^2), median (i.q.r.)	24.4 (23–27)	25.2 (23–28)	0.307†
Cirrhosis	1 (3)	12 (8)	0.257
Diabetes	4 (10)	28 (18)	0.270
Type of tumour			0.515
CRLM	19 (49)	85 (53)	
HCC	4 (10)	11 (7)	
IHCC	4 (10)	22 (14)	
PHCC	5 (13)	25 (15)	
GBCA	4 (10)	9 (6)	
Other	3 (8)	8 (5)	
Neoadjuvant chemotherapy	19 (49)	77 (48)	0.758
FOLFOX/XELOX	14 (74)	50 (65)	
FOLFIRI/XELIRI	2 (11)	13 (17)	
FOLFIRINOX	2 (11)	10 (13)	
Other	1 (5)	4 (5)	
Biological agent	13 (68)	60 (71)	0.766
Bevacizumab	4 (31)	39 (65)	
Cetuximab/ panitumumab	9 (69)	21 (35)	
Volumetric data			
sFLR1, median (i.q.r.)	18 (16–23)	19 (15–25)	0.804†
Interval from intervention to first volumetry (days), median (i.q.r.)	17 (13–32)	24 (19–37)	0.009†
sFLR2, median (i.q.r.)	31 (24–39)	28 (21–37)	0.102†
% hypertrophy, median (i.q.r.)	59 (4579)	48 (24–69)	0.020†
Kinetic growth rate during interval from intervention to first volumetry (per week), median (i.q.r.)	3.5 (2.2–7.1)	2.5 (1.1–3.8)	< 0.001†

Values are *n* (%) unless otherwise indicated. PVE, portal vein embolization; HVE, hepatic vein embolization; CRLM, colorectal liver metastasis; HCC, hepatocellular carcinoma; IHCC, intrahepatic cholangiocarcinoma; PHCC, perihilar cholangiocarcinoma; GBCA, gallbladder cancer; FOLFOX, 5-Fluorouracil/Oxaliplatin; XELOX, Capecitabine/Oxaliplatin; FOLFIRI, 5-Fluorouracil/Irinotecan; XELIRI, Capecitabine/Irinotecan; FOLFIRINOX, 5-fluorouracil/Irinotecan/Leucovorin/Oxaliplatine; sFLR, standardized future liver remnant. *χ^2 or Fisher's exact test, except †Mann–Whitney *U* test.

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Table 2 Operative clinical data and oncological outcomes

	PVE/HVE ($n = 39$)	PVE ($n = 160$)	P*
Resection			0.007
Feasible	36 (92)	109 (68)	
Failed	3	51	
Progression of disease	2 (67)	31(61)	
Insufficient liver growth	0 (0)	17(33)	
Postinterventional complications	1(33)	3(6)	
Interval from intervention to resection (days), median (i.q.r.)	37 (21–52)	41 (28–61)	0.132†
Type of resection			< 0.001
Right hepatectomy	5 (14)	55 (50)	
Extended right hepatectomy	30 (83)	50 (46)	
Left hepatectomy	0 (0)	2 (2)	
Extended left hepatectomy	1 (3)	2 (2)	
Duration of operation (min), median (i.q.r.)	321 (210–443)	385 (311–435)	0.044†
Blood loss (ml), median (i.q.r.)	800 (500–1450)	650 (400–1500)	0.708†
Major complications (≥ Clavien–Dindo IIIA)	9 (23)	37 (34)	0.546
PHLF according to ISGLS criteria	4 (10)	27 (25)	0.145
Death within 90 days after resection	1 (3)	17 (15.6)	0.065
Oncological outcomes			
Negative resection margin, R0	28 of 36 (78)	85 of 109 (78)	0.615
Follow-up time (months), median i.q.r.)	32	17	0.652‡
Recurrence	18/36 (50)	56/109 (51)	0.559
Death	12 (31)	91 (57)	0.003
Tumour-related death	8 (21)	74 (47)	0.196
Further treatment	26 (67)	69 (43)	0.307
Adjuvant/palliative chemotherapy	22 (56)	51 (32)	
Surgery for recurrent liver disease	6 (15)	12 (8)	
Ablation of liver	5 (13)	17 (11)	
Median overall survival (months)	Not reached	20	0.004‡
Median progression-free survival	19	11	0.088‡

Values are n (%) unless otherwise indicated. PVE, portal vein embolization; HVE, hepatic vein embolization; PHLF, posthepatectomy liver failure; ISGLS, International Study Group of Liver Surgery; *χ^2 or Fisher's exact test, except †Mann–Whitney U test and ‡log rank test.

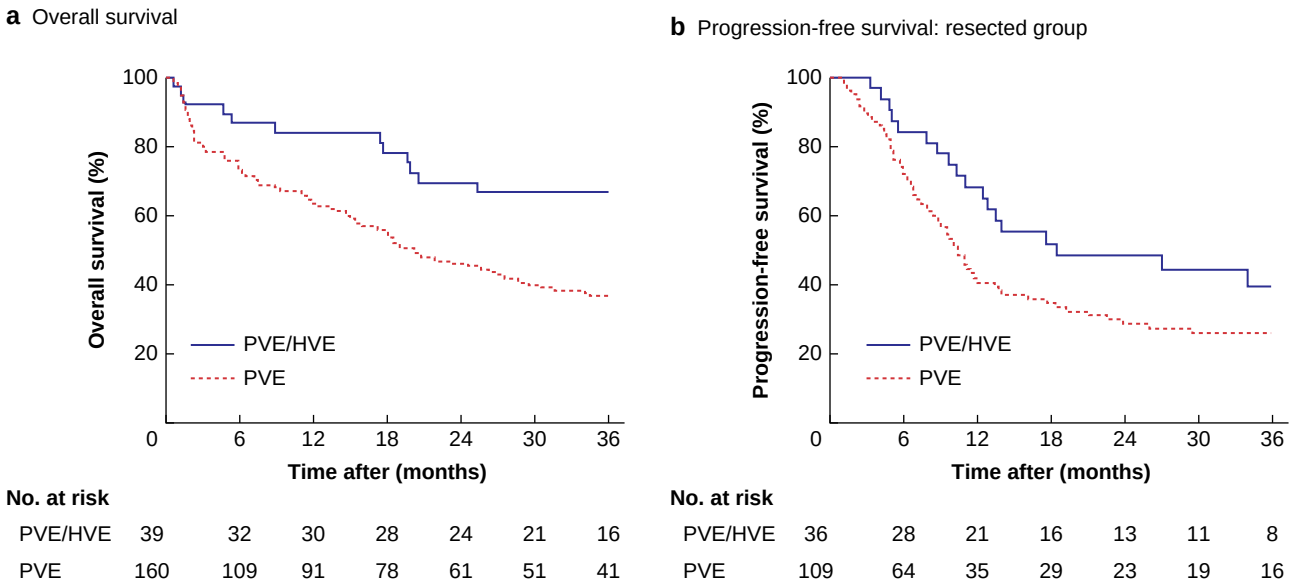


Fig. 2 Overall survival, and progression-free survival among patients who underwent resection (total group)

a Overall survival, and **b** progression-free survival among patients who underwent resection. PVE, portal vein embolization; HVE, hepatic vein embolization. **a** $P = 0.004$, **b** $P = 0.088$ (log rank test).

Survival

Of the 199 included patients, 19 (10%) were lost to follow-up (4 in the PVE/HVE group and 15 in the PVE-alone group) with respect to the endpoint survival before 36 months. These patients were mainly from referral centres and were marked as censored. Median follow-up was 32 and 17 months after PVE/HVE and PVE respectively (*Table 2*). In the PVE/HVE group, median overall survival was not reached within 36 months, compared with a median survival time of 20 months after PVE alone ($P = 0.004$) (*Fig. 2*). Recurrence/progression-free survival did not differ significantly between the groups.

Patients who did not undergo surgical resection following PVE/HVE and PVE had significantly worse overall survival ($P < 0.001$) (*Fig. S1*). In a survival analysis excluding 90-day deaths, PVE/

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Table 3 Univariable analysis of overall survival for treatment group (portal vein embolization *versus* portal vein embolization/hepatic vein embolization)

	HR	P
Treatment group (PVE/HVE *versus* PVE)	0.46 (0.27, 0.76)	0.003

Values in parentheses are 95% confidence intervals. The analysis included 197 patients. PVE, portal vein embolization; HVE, hepatic vein embolization.

Table 4 Multivariable analysis of overall survival for five variables

	HR	P
Treatment group (PVE/HVE *versus* PVE)	0.57 (0.33, 0.99)	0.047
Age (years) (continuous)	1.04 (1.02, 1.06)	< 0.001
Diabetes (yes *versus* no)	1.10 (0.68, 1.78)	0.701
Cirrhosis (yes *versus* no)	1.08 (0.51, 2.28)	0.840
CRLM (yes *versus* no)	1.11 (0.77, 1.61)	0.575

Values in parentheses are 95% confidence intervals. The analysis included 197 patients. HR for continuous variables are shown per unit increase, PVE, portal vein embolization; HVE, hepatic vein embolization; CRLM, colorectal liver metastasis.

HVE remained superior to PVE alone ($P = 0.014$) (*Fig. S2*). Survival analysis of the 1 : 1 matched subgroup also showed improved survival for PVE/HVE compared with PVE alone ($P < 0.001$) (*Fig. S3*).

Multivariable analysis for survival

Univariable Cox regression analysis was undertaken to assess the effect of the intervention (PVE/HVE) compared with the control treatment (PVE) on the mortality rate within 36 months. The HR in this analysis was 0.46 (95% c.i. 0.27 to 0.76; $P = 0.003$) (*Table 3*). Two multivariable analyses were also undertaken for the endpoint survival (*Tables 4* and *5*). To correct for the time of inclusion (time of embolization), to check the era bias, another multivariable analysis was conducted (*Table 6*). In the first multivariable analysis, patient age, diabetes, cirrhosis, and CRLM were included in addition to the treatment group variable (PVE *versus* PVE/HVE), while maintaining an appropriate sample size (197 patients). All these factors might be related to survival. The HR for PVE/HVE *versus* PVE alone was 0.57 (0.33 to 0.99; $P = 0.047$). In the second multivariable analysis, major complications (at least Clavien–Dindo grade IIIA), complete tumour resection (R0), and blood loss were also included in the model. Owing to missing data in both groups, the cohort size decreased to 145 after including these additional factors. The HR for PVE/HVE *versus* PVE in this analysis was 0.50 (0.26 to 0.95; $P = 0.034$). In the two multivariable analyses, age and major complications seemed to have an independent, negative effect on survival. Finally, the HR for PVE/HVE *versus* PVE in the analysis corrected for year of inclusion was 0.47 (0.24 to 0.92; $P = 0.027$). Year of inclusion seemed to have no effect on overall survival, with an HR of 0.95 (0.78 to 1.17; $P = 0.650$).

Subgroup analysis of colorectal liver metastasis

The Charlson Co-morbidity Index score and the percentage of patients who underwent two-stage hepatectomy (TSH) were higher in the PVE group in the subgroup of patients with CRLM (*Table S1*). The KGR was higher after PVE/HVE, whereas the resection rate did not differ significantly between PVE/HVE and PVE alone in this subgroup analysis. After a median follow-up of 34 months (PVE/HVE) and 20 months (PVE), which did not differ statistically ($P = 0.123$), median overall survival was not reached

Table 5 Multivariable analysis of overall survival for eight variables

	HR	P
Treatment group (PVE/HVE *versus* PVE)	0.50 (0.26, 0.95)	0.034
Ages (years) (continuous)	1.03 (1.01, 1.06)	0.007
Diabetes (yes *versus* no)	1.02 (0.54, 1.93)	0.949
Cirrhosis (yes *versus* no)	1.99 (0.57, 6.89)	0.280
CRLM (yes *versus* no)	0.96 (0.59, 1.54)	0.851
Major complications, Clavien–Dindo ≥ IIIa (yes *versus* no)	2.79 (1.76, 4.44)	< 0.001
Blood loss (ml) (continuous)	1.00 (1.00, 1.00)	0.467
R0 (yes *versus* no)	0.65 (0.38, 1.10)	0.108

Values in parentheses are 95% confidence intervals. The analysis included 145 patients. HR for continuous variables are shown per unit increase, PVE, portal vein embolization; HVE, hepatic vein embolization; CRLM, colorectal liver metastasis.

Table 6 Multivariable analysis of overall survival for treatment group (portal vein embolization *versus* portal vein embolization/hepatic vein embolization) with correction for year of intervention

	HR	P
Treatment group (PVE *versus* PVE/HVE)	0.47 (0.24, 0.92)	0.027
Year of inclusion/intervention	0.95 (0.78, 1.17)	0.650

Values in parentheses are 95% confidence intervals. The analysis included 196 patients. PVE, portal vein embolization; HVE, hepatic vein embolization.

in the PVE/HVE group, whereas it was 26 months in PVE-alone group ($P = 0.036$) (*Fig. S4*). There was no significant difference in recurrence/progression-free survival between the two treatments among patients with resected CRLM (median 19 months for PVE/HVE *versus* 11 months for PVE; $P = 0.077$). Patients who did not undergo surgical resection after PVE/HVE and PVE had significantly worse overall survival ($P < 0.001$) (*Fig. S5*).

Discussion

Along with increased FLR hypertrophy and resection rate, and despite a variety of potential biases owing to the retrospective design, in the present study PVE/HVE was associated with significantly better overall survival than PVE alone in patients with liver cancers and in a subgroup of patients with colorectal liver metastases. The findings support the need for the recently initiated prospective international multicentre RCTs comparing PVE/HVE *versus* PVE in CRLM alone (DRAGON 2 trial; NCT05428735) and in primary liver cancers (DRAGON PLC).

Patients who did not undergo liver resection after PVE/HVE or PVE alone had significantly worse survival than those who had surgical resection. Univariable and multivariable Cox regression analyses for the endpoint survival demonstrated that PVE/HVE was associated with survival with HRs of between 0.46 and 0.57.

The reason why patients who had PVE/HVE lived longer in this study is most likely multifactorial: a higher resection rate owing to the rapid hypertrophy following PVE/HVE, the lower 90-day mortality rate after resection, and an increased depth of oncological response by a higher proportion of extended resections. Although, the KGR was significantly higher in the PVE/HVE group, the sFLR2 did not differ between groups. The significance of rapid liver growth and an increased resection rate was first demonstrated in the ALPPS arm of the LIGRO trial[10]. In LIGRO, the resection rate and median overall survival were significantly improved in patients undergoing ALPPS

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compared with TSH (46 *versus* 26 months respectively; $P = 0.028$)[25]. ALPPS in LIGRO allowed resection in 92% *versus* 57% of patients in the TSH arm ($P < 0.001$). This increased resection rate resulted directly in improved survival on long-term follow-up. Similarly, the present study has now also shown that the previously reported feasibility of resection rate of 92% in the PVE/HVE group compared with 68% in the PVE arm translated into improved median survival time in the PVE/HVE arm. However, it needs to be emphasized that this study was retrospective, whereas LIGRO had prospectively randomized cohorts. Furthermore, the present study included a variety of tumour aetiologies, whereas only patients with CRLM and neoadjuvant chemotherapy were included in LIGRO. In contrast, 9% of patients with CRLM in the PVE group did not receive neoadjuvant chemotherapy in the present study. Although a recent meta-analysis[18] revealed a pooled resectability rate of 87% after PVE/HVE, the resectability rate following PVE/HVE here (92%) was relatively high compared with that reported by other studies[26,27] which described lower resection rates. Nevertheless, the general gist of the present findings in this study is very similar to the median-term survival data presented by LIGRO. The findings might also suggest that an initial more extensive reduction of cancer mass in the liver leads to improved median survival in patients with a variety of tumour aetiologies.

In contrast, patients who did not undergo surgical resection had significantly worse survival. Brouquet *et al.*[28] were the first to show the oncological relevance of successful completion of a two-stage strategy in a retrospective analysis of patients with CRLM. Non-completion of a two-stage procedure and major complications were revealed as the only predictors of survival. LIGRO was the first study to confirm these retrospective findings in a randomized study. In line with both studies, the multivariable analysis here showed that PVE/HVE is an independent predictor for survival, and that accelerated liver growth and a higher resection rate are associated with better survival.

There was no difference in recurrence/progression-free survival between treatment groups. It may appear contradictory that overall survival differed significantly, but not recurrence/progression-free survival. However, the finding can be explained by the lower resectability rate in PVE, as these patients had significantly worse overall survival. The lack of difference in recurrence/progression-free survival can also be explained by the lower resectability rate in PVE. If significantly more patients are unable to undergo surgical resection after PVE alone, there are fewer patients to develop recurrence.

The initial enthusiasm for ALPPS neglected an important downside of the rapid hypertrophy in that procedure: its maximally invasive surgical approach in stage 1 of the TSH. Even the first ALPPS series revealed an incidence of Clavien–Dindo grade III and IV complications of 44% and an in-house mortality rate of 12%[12]. Later studies even reported a 90-day mortality rate of 15–48%[13,14,29–31], especially in elderly patients and those with primary liver tumours[14]. Despite increased selection of patients and the preferential use of ALPPS in CRLM in the following years, morbidity and mortality rates have remained comparatively high[10,32,33].

Despite the resection rate of 68% after PVE, which is slightly lower than in previously published studies, survival after PVE demonstrated here remained very similar to that in other studies[8,25]. As experience with HVE is growing, this procedure is increasingly being used as a salvage or rescue procedure after PVE in patients with insufficient FLR hypertrophy. The initiation of a high FLR hypertrophy rate by limiting the formation of intrahepatic collaterals with simultaneous PVE/HVE allows a shorter interval between embolization and resection.

The general feeling is that a simultaneous embolization procedure will be superior to a staged/sequential procedure. Whether survival after staged/sequential PVE/HVE is comparable to simultaneously performed PVE/HVE remains unknown.

This study has several limitations. First, the retrospective design and the absence of independent monitoring may have introduced reporting bias. However, by close collaboration, an attempt was made to keep these sources of bias as small as possible. Moreover, as a result of the retrospective design, there was variation in embolization techniques, and resectability was not defined homogenously among participating centres. Second, selection bias cannot be completely ruled out, but was probably minimal as all patients undergoing embolization in participating centres within the time period analysed were included. However, because of the younger age, shorter operating time, lower Charlson Co-morbidity Index score, and smaller number of two-stage resections in the CRLM subgroup, there seemed to be a selection bias for extended resections in the PVE/HVE group. Third, an era bias cannot be excluded because PVE/HVE as the newest regenerative procedure has been mainly performed in recent years. Embolization techniques have changed during the long observation period. In recent years, glue has been used increasingly for PVE (especially in the PVE/HVE group) as glue was shown to be superior to other embolic agents regarding the induction of liver hypertrophy[34]. However, microparticles were still used in some patients in the PVE-alone group. In addition, treatment options for intrahepatic or extrahepatic recurrence have become increasingly aggressive over time. Furthermore, the definition of technical resectability and the need for regenerative liver surgery have changed over study interval. Although a sFLR of 20% was originally accepted as threshold for safe liver resection, a cut-off of 25–30% has become accepted more in recent years.

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

Deidentified data are available upon reasonable request.

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