Safety and efficacy of combined portal and hepatic vein embolisation in patients with colorectal liver metastases (DRAGON1): a multicentre, single-arm clinical trial

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Summary

Background **Major liver resection is often required for complete clearance of colorectal liver metastases (CRLM). Patients with insufficient future liver remnant (FLR) volume/function are at high risk of post-hepatectomy liver failure (PHLF) and require FLR hypertrophy-inducing procedures to enable safe resection. The most recent variant of these procedures is combined portal and hepatic vein embolization (PVE/HVE). The DRAGON 1 trial evaluates the safety and efficacy of PVE/HVE, while assessing recruitment potential for the DRAGON 2 randomized trial.**

Methods DRAGON 1 is a prospective, single-arm, international, multicenter trial. Patients with upfront unresectable CRLM due to a small FLR were included. The primary outcome was the ability of centers to recruit three patients and perform PVE/HVE and liver resection without 90-day mortality. Secondary outcomes included recruitment capacity, PVE/HVE technical details, FLR volume changes, complications, and resection rates. The study is registered at ClinicalTrials.gov, identifier: NCT04272931.

Findings In total, 102 patients were included from 43 centers. Twenty-four centers (24/43 = 56%) recruited three or more patients, and 20 centers (20/43 = 47%) achieved this without 90-day mortality. Of 96 patients undergoing PVE/HVE, no post-embolization mortality occurred, though major complications were reported in two patients. Resection was completed in 86 patients (86/96 = 90%), with seven patients (7/86 = 8%) dying within 90 days. PHLF grade B/C (International Study Group of Liver Surgery criteria) occurred in 19 patients (19/86 = 22%).

Interpretation DRAGON 1 demonstrates that PVE/HVE is safe, with no embolization-related mortality, low morbidity, and high resection rates in upfront unresectable CRLM.

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Keywords: Portal vein embolization; Hepatic vein embolization; Liver venous deprivation; Colorectal liver metastases; Future liver remnant; Liver resection; FLR hypertrophy; Kinetic growth rate; Post-hepatectomy liver failure; Liver surgery complications; Hepatic regeneration; Multicenter clinical trial; Resection rates; Embolization techniques; Extended liver resection; Regenerative liver procedures; DRAGON 1 trial; Preoperative liver augmentation; Surgical oncology; Bilobar colorectal liver metastases

Research in context

Evidence before this study

An extensive systematic literature search was conducted in PubMed, Web of Science, and Embase. The search was performed in September 2022, with no restrictions on date of publication. Search terms included "colorectal liver metastases", "portal and hepatic vein embolization", and "future liver remnant". A total of six case series and eight comparative studies examining combined portal and hepatic vein embolization (PVE/HVE) versus portal vein embolization alone (PVE) were identified. All studies were retrospective and of weak or moderate quality, with most involving small sample sizes. Eleven studies reported on 90-day mortality after embolization followed by resection, with a 6·9% mortality rate in the single-arm PVE/HVE studies (12/175), and a 2·2% rate in the PVE/HVE arm of the comparative studies. Resection rates after PVE/HVE ranged from 64 to 94%, with pooled resection rates of 83% in single-arm studies and 87% in comparative studies.

Added value of this study

The DRAGON 1 trial is the largest international, multicenter, prospective single-arm trial to date examining the implementation, safety, and efficacy of PVE/HVE. As PVE/HVE, despite higher costs, gains popularity worldwide and its adoption in clinical practice increases, the need for prospective evidence has become more pressing. The findings of the DRAGON 1 trial are unique and significant, as it is the only completed international, prospective study focusing on the safety of PVE/HVE.

Implications of all the available evidence

The results of the DRAGON 1 trial confirm the safety of the PVE/HVE procedure, consistent with previous retrospective evidence. The trial demonstrates low morbidity, no embolization-related mortality, as well as a high resection rate of 90%. Current evidence is promising, suggesting PVE/HVE may surpass PVE alone in terms future liver remnant hypertrophy, resection rates, and even long-term survival. However, high-quality randomized controlled trials are needed to definitively position the role of PVE-HVE in daily practice. Additionally, post-hepatectomy liver failure (PHLF) remains a significant challenge, with 22% of resected patients developing Grade B/C PHLF, contributing to an 8% 90-day mortality rate. This suggests that current FLR assessments may fall short in preventing PHLF, emphasizing the need for more precise preoperative evaluation. The DRAGON 1 trial also served as an accrual test for the currently accruing DRAGON 2 trial, which investigates PVE/HVE efficacy in CRLM patients in a randomized comparison with the current standard of PVE alone.

Introduction

Surgical resection and ablation are the cornerstones of the curative treatment strategy in patients with multiple colorectal liver metastases (CRLM). Long-term survival or cure can be achieved by complete tumor resection in variants of one- or two-stage hepatectomy, eradication by multiple metastasectomies and/or thermal ablation.

Patients with CRLM undergoing major liver resection face a relatively high post-operative morbidity, with mortality rates ranging from 7% to 11%.[1–4] Consequently, liver parenchyma-sparing surgery (PSS) has become the strategy of choice over the past decade. Yet, PSS often requires repeated resections/oncological interventions to sustain disease control and long-term survival.[5] The concept of PSS is also difficult to apply in patients with extensive bilobar disease. To achieve complete clearance of all metastases in these cases, major anatomical liver resections must frequently be performed in patients with a relatively small or borderline Future Liver Remnant (FLR) volume. To allow safe resection and reduce the risk of post-hepatectomy liver failure (PHLF), sufficient volume and, more importantly, sufficient function of the FLR are crucial.[6]

FLR hypertrophy-inducing procedures like Portal Vein Embolization (PVE) or Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS) are used to enhance the functional capacity of the FLR prior to major liver resection in patients with upfront unresectable CRLM, with PVE being the current clinical standard. FLR function is generally estimated by calculating the ratio of FLR volume to (standardized) total liver volume (TLV) and by assessing the Kinetic Growth Rate (KGR) of the FLR three to four weeks after PVE.[7] More precise functional assessment of the FLR, using 99 mTc-mebrofenin hepatobiliary scintigraphy (HBS), has been shown to be an effective tool in determining resectability and preventing PHLF and mortality after resection. HBS is gaining interest and is advocated in expert consensus guidelines but yet to be widely adopted.[8]

About one third of patients that undergo PVE remain unresected, predominantly due to insufficient FLR hypertrophy or tumor progression during the waiting time after embolization.[9,10] This remains a key challenge in the treatment of patients with upfront unresectable CRLM and points out the need for strategies beyond PVE to ensure fast and adequate increase in FLR volume/function before tumor progression occurs.

Combined Portal and Hepatic Vein Embolization (PVE/HVE), a variant of Liver Venous Deprivation (LVD), by percutaneous occlusion of one or two ipsilateral hepatic veins simultaneously with PVE, has been shown to accelerate FLR hypertrophy and to improve the degree of hypertrophy (DH) and KGR.[11,12] Recent data suggest that it may also raise resection rates and survival compared to PVE alone.[13] However, published series on PVE/HVE have predominantly been retrospective and emphasize efficacy over safety.[14,15]

The prospective, international, multicenter DRAGON 1 trial sought to assess safety and efficacy of PVE/HVE in patients with upfront unresectable CRLM in need of conversion chemotherapy and FLR-augmentation to undergo liver resection. The trial also assessed accrual potential of participating centers in preparation for the prospective randomized controlled DRAGON 2 trial comparing PVE/HVE and PVE alone in patients with upfront unresectable CRLM.

Methods

Study design

This study was a phase II, prospective, single-arm, international, multicenter trial primarily designed to identify potential risks of PVE/HVE and subsequent resection, and to identify annual accrual potential of participating centers in preparation for the DRAGON 2 randomized trial. The study protocol was designed in a multidisciplinary setting, using two Delphi rounds and consensus among surgeons and interventional radiologists from the DRAGON trials collaborative.[16]

Patient selection and study sites

Patients were recruited at 43 centers from 14 countries in North America, Europe, Australia, and Asia from May 2020 to November 2022. Participating centers included both university and regional hospitals, all of which had specialized Hepato-Pancreato-Biliary (HPB) units. Details regarding the participating centers are provided in Supplementary Table S1.

Patients were 18 years of age or older with upfront unresectable CRLM after conversion chemotherapy due to a small FLR, defined as < 30% in normal livers or <40% in chemotherapy-damaged livers. All patients and their treatment strategies were evaluated at local multidisciplinary tumor board (MDT) meetings. Patients with progression of disease after conversion chemotherapy according to RECIST criteria were excluded.[17] Both patients with metachronous and synchronous CRLM were included. Patients with extrahepatic metastases were eligible for inclusion only if treatment of extrahepatic disease with curative intent was possible and intended. Treatment of the primary colorectal carcinoma was not standardized. Details on inclusion and exclusion criteria are provided in the study protocol [Supplementary Document 1].

Ethics and privacy

The study is reported in compliance with the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement and performed in accordance with the Declaration of Helsinki.[18,19] The trial protocol was approved by the ethics committee at each site and has been published previously.[16] All patients or their legal representatives provided written informed consent before participation. After informed consent was

provided, patients were assigned a unique, automatically generated Study ID. Personal data linking patients to their Study ID was password-protected and securely stored at the local study sites. The study is registered at ClinicalTrials.gov, identifier: NCT04272931.

Data collection

Baseline characteristics, Digital Imaging and Communications in Medicine (DICOM) imaging data, procedural details of embolization and surgery, complications, post-procedural hospital stays, laboratory findings, and follow-up data at one, three, six, and twelve months after resection were pseudonymized and registered by the local teams using Castor Electronic Data Capture software (Castor EDC, Amsterdam, The Netherlands). Details on timing of data points are presented in Supplementary Figure S1.

Intervention

Per protocol, PVE/HVE involved percutaneous embolization of the portal vein to one liver side and occlusion of the ipsilateral hepatic vein, with additional embolization of the middle hepatic vein and portal vein to segment 4 encouraged in cases requiring extended hepatectomy. To minimize the risk of non-targeted embolization of the FLR, PVE was performed prior to the HVE procedure.[20] Performing PVE and HVE within one session was recommended, however, a maximum of 48 hours between PVE and HVE was allowed. At the time of inclusion start, there were no available data proving that a staged procedure could be less effective. Within this study, PVE was performed according to the local standard of care. For HVE, the occlusion of the hepatic veins was performed by placement of at least one vascular plug per hepatic branch, predominantly the Amplatzer™ Vascular Plug II (Abbott Laboratories, Chicago, Ill, USA). To prevent untargeted embolization of the lungs, the use of glue inside the hepatic vein(s) or collaterals was, in contrast to the Liver Venous Deprivation strategy as described by Guiu et al., not allowed.[14] To minimize the risk of plug migration, 50% oversizing of the vascular plug with respect to the target vessel diameter was advised. A DRAGON collaborative consensus-based work instruction for the PVE/HVE procedure was provided to all participating centers before site initiation [Supplementary Document 2]. Additionally, online or onsite proctoring by an experienced Interventional Radiologist was offered to all centers by the trial coordinators.

FLR volumetry

Baseline and post-embolization FLR volumes were measured at the local centers using CT or MRI at four standardized time points: pre-PVE/HVE, and one week, three weeks, and six weeks after PVE/HVE. The volumetric assessments at three- and six-weeks post-embolization were conducted only if the FLR was deemed insufficient for resection at the preceding measurement. Once the FLR was considered sufficient by the local team, the patient was offered liver surgery. Assessment of changes in the FLR volume were standardized (sFLR) by calculating the ratio of the FLR to the Standardized Total Liver Volume (sTLV) using the Vauthey formula.[21] The DH was calculated as the percentage point difference in sFLR volume at the predefined time points. The KGR was determined from the DH, quantifying the weekly percentage volume increase observed in subsequent measurements. Definitions and formulas used to present the volume data can be found in Supplementary Table S2.

Functional assessments, including HBS, indocyanine green (ICG) clearance test and LiMAx were not protocolized due to their limited availability in participating centers during the study.

Liver resection

Resection nomenclature followed the Brisbane classification.[22] An anatomical major hepatectomy is any resection involving three or more adjacent segments, regardless of location. Surgical strategy regarding one- or two-stage resections was at the discretion of local centers. Waiting time was defined as the time in days between PVE/HVE and resection.

Primary outcome

The primary outcome at the start of this study was the ability of each participating center to recruit three patients for PVE/HVE in 12 months and safely perform the procedure including the liver resection, without 90-day mortality after resection due to complications. Due to COVID-19, most clinical research projects in participating centers were paused. Consequently, the 12-month inclusion limit was unfeasible and therefore altered. The modified primary outcome was: the ability of each participating center to recruit 3 patients for PVE/HVE and safely perform the procedure including the liver resection, without 90-day mortality after resection due to complications.

Secondary outcomes

PVE/HVE technique

Details regarding the PVE/HVE intervention were assessed, including venous access approach, embolization materials, vessels embolized, intervention time, and simultaneous versus staged approach.

Recruitment capacity

Recruitment capacity was evaluated by a participating center's ability to enroll three patients both within one year and within the full accrual period for all centers.

Safety

Morbidity within 90-days after PVE/HVE and after liver resection was assessed using the Clavien-Dindo (CD)

classification.[23] PHLF was assessed based on the criteria established by the International Study Group of Liver Surgery (ISGLS), categorizing patients as either grade A, B or C to determine the severity of liver dysfunction following surgery.[24]

Resectability

Resectability was defined as a complete resection of all metastases using a major hepatectomy regardless of preoperative sFLR volume. Exploration-only procedures did not qualify as resection. FLR cut-offs for resection were determined per individual patient by the local team at participating centers.

Radiological resectability was evaluated using post-embolization CT/MRI volumetry and was defined as sFLR ≥30% in normal livers or ≥40% in livers damaged by chemotherapy.

Oncological outcomes

Data on systemic treatment, resection margin status, and full clearance of all liver metastases were recorded. Only outcomes until 90-days follow-up are reported within this paper.

Protocol deviations

Deviations from the protocol were observed in relation to the HVE occlusion materials in six patients. Specifically, vascular plugs and glue were used in six patients, while a combination of vascular plugs, coils, and glue was used in one patient. Additionally, deviations occurred in the timing of FLR volumetry; due to logistical constraints, CT scans could not be conducted within the protocol-specified time windows (day 7, day 21, and day 42 ± 1 day) for all patients.

Statistics

Initially, a sample size of 75 patients was set to allow proper evaluation of safety and accrual within a reasonable time. This sample size was based on three inclusions per center from the 25 centers that were initially expected to participate. The sample size was later revised to 120 patients due to an increase in the number of participating centers to 40. All data on primary and secondary outcomes are presented as descriptive statistics with interquartile ranges (IQR), unless otherwise specified. Confidence intervals (95% CI) were calculated using the Wilson method including continuity correction.

Funding

The funders of the DRAGON 1 trial are: The Dutch Cancer Society, National Institute for Health and Care Research UK, Maastricht UMC+, Abbott Laboratories and Guerbet. All funding was non-restrictive and used for trial coordination. The funders had no role in study design, data collection, data analysis, data interpretation, or the writing of the report.

Results

Patients

A total of 102 patients were enrolled in the study. Six patients were not included in the analysis as they never underwent the study intervention. Three dropouts were due to disease progression before the intervention, one patient dropped out because the FLR was deemed sufficient for upfront resection, and two patients were transferred before the intervention to non-participating hospitals (Fig. 1). The median age was 62 years (IQR 53–70), 54 (56%) of the participants were male and 42 (44%) were female. Patient demographics are presented in Table 1.

Primary outcome

Twenty centers (47%) included 3 patients without 90-day postoperative mortality. There was no 90-day mortality after PVE/HVE. Of the 96 patients that underwent PVE/HVE, 86 patients (90% [95% CI 81–95]) underwent surgical resection. Of these, seven patients (8% [95% CI 4–17]) died within the first 90 days after resection. Therefore, seventy-nine patients (82% [95% CI 73–89]) underwent PVE/HVE and resection with 90-day survival.

Secondary outcomes

PVE/HVE technique

Eighty-nine patients (93%) underwent PVE and HVE in the same session. The median PVE/HVE procedure time was 135 min (IQR 101–165). N-butyl cyanoacrylate/Lipiodol (glue) was most frequently used as embolization material for PVE (66%). HVE was performed using vascular plugs only in 75 patients (78%). Additional procedure details can be found in Table 2.

Recruitment capacity

Forty-three centers obtained ethical approval and were initiated for trial participation and patient accrual. Twenty-four centers (56%) included three or more patients, 13 centers (30%) included one or two patients, and six centers (14%) did not include any patients (Fig. 1).

Safety of PVE/HVE

One CD grade IV procedure-related and one grade III potentially procedure-related serious adverse event were observed after PVE/HVE. The former involved the migration of an undersized vascular plug into the pulmonary artery, necessitating cardiothoracic surgery, further complicated by post-operative bleeding. The latter entailed a patient with no history of portal hypertension or cirrhosis who suffered from esophageal variceal hemorrhage requiring endoscopic rubber band ligation. All remaining adverse events following PVE/HVE (n = 17) were either grade I (in 11 patients, 11%) or grade II (in six patients, 6%). These PVE/HVE-related adverse events were 11 post-embolization syndromes

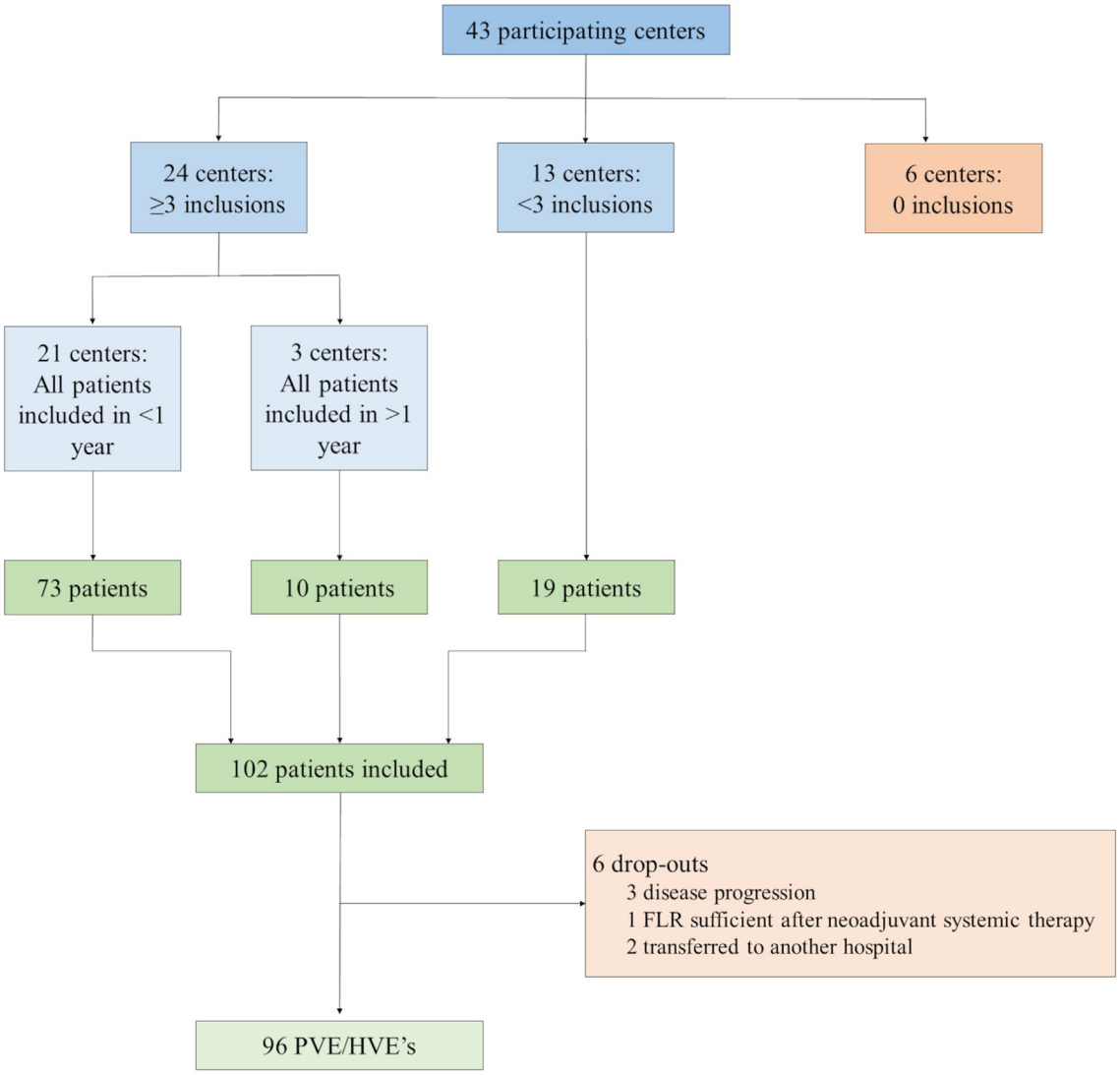

Fig. 1: Flow diagram of patients included. Footnote: FLR: future liver remnant; PVE/HVE: combined portal and hepatic vein embolization.

(11%), two glue migrations (2%), two intra-abdominal hematomas (2%), one portal venous thrombosis (1%), and one swelling at the jugular venous access site (1%). There were three post-embolization adverse events that were unrelated to PVE/HVE: two cases of colon obstruction due to primary tumor progression, and one case of SARS-CoV-2.

Safety of resection

Forty-six patients (53%) out of 86 resected patients underwent an extended hemi-hepatectomy, the remaining 40 patients (47%) underwent a regular left or right hemi-hepatectomy. Complications after surgery were observed in 49 of the 86 resected patients (57%), with 30 patients (35%) experiencing complications CD grade III or higher. Early postoperative mortality occurred in three patients due to iatrogenic portal vein injury and acute small-for-size syndrome in one, acute liver and respiratory failure in the second, and intraoperative blood loss of 1500 milliliters (mL) followed by cardiopulmonary resuscitation and multiorgan failure in the third. The remaining four mortality cases occurred on postoperative days 43, 51, 58, and 73, and were attributed to PHLF. Nineteen of the 86 patients (22%) that underwent resection had PHLF Grade B (n = 11) or Grade C (n = 8). A comprehensive overview of PHLF cases is presented in Supplementary Table S3. In Supplementary Table S4, post-resection morbidity and mortality are shown per center type based on accrual capacity: centers that were able to include three or more

All patients	PVE/HVE
	96
Age (years), median (IQR) (range)	62 (53–70) (34–78)
Sex, male, n (%)	54 (56)
BMI (kg/m^2), median (IQR) (range)	25·3 (22·4–27·8) (16·6–42·8)
Diabetes, n (%)	12 (13)
ECOG[a], n (%)	
ECOG 0	81 (85)
ECOG 1	14 (15)
Location of primary tumor, n (%)	
Left-sided Colon	43 (45)
Right-sided Colon	26 (27)
Rectum	27 (28)
Synchronous liver metastases, n (%)	74 (77)
Liver first strategy	49 (51)
Two stage strategy, FLR cleaning, n (%)	38 (40)
Resection only	24 (63)
Resection combined with ablation	11 (29)
Percutaneous ablation	3 (8)
Number of metastases in liver, median (IQR) (range)	7 (4–12) (1–27)
Extrahepatic disease, n (%)	8 (8)
Neoadjuvant systemic therapy[b], n (%)	94 (98)
FOLFOX	50 (53)
FOLFIRI	16 (17)
FOLFOXIRI	20 (21)
CAPOX/XELOX	14 (15)
Bevacizumab	36 (38)
Cetuximab	6 (6)
Panitumumab	15 (16)
Other	11 (12)

IQR; interquartile range; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group performance status; FLR: future liver remnant. [a]ECOG status was unavailable for 1 patient. [b]Data regarding neoadjuvant systemic therapy was unavailable for 1 patient.

Table 1: **Patient demographics.**

All patients	PVE/HVE
	96
PVE/HVE in one session, n (%)	89 (93)
PVE/HVE in two sessions with max. 48-hour interval, n (%)	7 (7)
PVE, n (%)	
Right portal vein	94 (98)
Left portal vein	2 (2)
Simultaneous segment 4 embolization, n (%)	15 (16)
Approach, n (%)	
Transhepatic ipsilateral	86 (90)
Transhepatic contralateral	7 (7)
Transsplenic	3 (3)
Materials, n (%)	
N-butyl cyanoacrylate + Lipiodol (glue) alone	63 (66)
Particles and coils only	11 (11)
Other	22 (23)
HVE, n (%)	
Right hepatic vein only	75 (78)
Middle hepatic vein only	2 (2)
Right + middle hepatic vein	11 (11)
Right hepatic vein + accessory hepatic vein	6 (6)
Left hepatic vein	2 (2)
Approach, n (%)	
Transjugular	70 (73)
Transhepatic	25 (26)
Transfemoral	1 (1)
Materials, n (%)	
Vascular plugs only	75 (78)
Vascular plugs and N-butyl cyanoacrylate + Lipiodol (glue)	5 (5)
Vascular plugs and coils	12 (13)
Vascular plugs, glue and coils	1 (1)
Coils only	2 (2)
Other	1 (1)
Intervention time in minutes, median (IQR) (range)[a]	135 (101–165) (24–333)

PVE: portal vein embolization; HVE: hepatic vein embolization; PVE/HVE: combined PVE and HVE. [a]73/96 patients could be analyzed for time of intervention, staged embolizations are excluded.

Table 2: **PVE/HVE procedure details.**

patients within one year (Group A) versus centers that included less than three patients (Group B), or were unable to include three patients within one year.

FLR volume changes

The median baseline FLR volume was 364 mL (IQR 276–456) and the median baseline sFLR was 23·5% (IQR 19·4–27·5). The median DH one week after PVE/HVE, equivalent to the KGR in the initial week, was 8·3 (IQR 4·3–12·4). The median sFLR at one week after PVE/HVE was 32·7% (IQR 27·3–38·4). Among the 70 patients not considered resectable after the week one assessment, the median DH between weeks one and three was 4·2 (IQR 1·3–7·2), the median KGR was 2·1 (IQR 0·7–3·6), and the median sFLR increased to 34·1% (IQR 29·7–39·5). Details of DH and KGR after one, three, and six weeks are depicted in Table 3 and Fig. 2.

Clinical resectability

A surgical resection with complete clearance of liver metastases was successfully performed in 86 patients (90%). Reasons for non-resection are depicted in Table 4. At week one post-embolization, 26 patients (27%) were scheduled for surgery. By the three-week assessment an additional 46 patients (48%) were scheduled for surgery. Sixteen more patients (17%) were scheduled for surgery after week six. One patient required a salvage parenchymal split (Split After Venous Embolization = SAVE) procedure four weeks after PVE/HVE in order to reach a sufficient sFLR to undergo resection.

Radiological resectability

Based on their last volumetric assessment before decision to resect, 15 patients (16%) had a sFLR <30%. Forty-seven patients (49%) had a sFLR between 30 and

39%, and an additional 34 patients (35%) had a sFLR ≥40%.

Discussion

This international prospective multicenter single-arm Dragon 1 trial shows that combined PVE/HVE can be performed safely in patients with upfront unresectable colorectal cancer liver metastases in need of conversion chemotherapy and FLR augmentation to undergo resection. PVE/HVE was shown to lead to a high degree of FLR hypertrophy with a rapid KGR, especially in the first week post-PVE/HVE. This resulted in a high resection rate with acceptable 90-day post-operative mortality, with PHLF being the predominant cause of post-operative death. The trial also shows a variable ability among centers to include three patients within 12 months, taking into account that accrual was hampered by inclusion stops during the COVID-19 pandemic.

The safety of PVE/HVE in this trial was shown by a low morbidity rate and the absence of embolization-related mortality, which is consistent with existing literature on morbidity after PVE alone, as well as earlier studies examining PVE/HVE.[13,25,26] The majority of complications after PVE/HVE were mild, while severe complications occurred in only two patients. One of these complications, a plug migration to the pulmonary artery, was directly related to the PVE/HVE procedure and caused by the use of an insufficiently (over)sized vascular plug. This stresses the importance of using at least 50% oversized vascular plugs for the embolization of the hepatic veins.

In this trial, a 90-day postoperative mortality rate of 8% was observed. It should be considered that all patients in this trial underwent major or extended liver resection, and that resection was performed after extensive chemotherapy and prior interventional manipulation of the liver. This rate is comparable to what is published in literature for CRLM, with mortality rates of 3–7% being observed after major resection, increasing to 10% after extended resection.[4,27] While using a new technique such as PVE/HVE, there may be a learning curve in the work-up, indication, timing, and execution of major or extended liver resection. Overcoming this learning curve could potentially lead to a reduction in post-operative mortality in future patients. Literature suggests lower liver surgery mortality rates at specialized, high-volume centers.[4,28] The DRAGON 1 trial was not designed to detect potential differences in mortality/morbidity between participating centers with high or low accrual capacity. Despite a higher mortality rate in centers with a low accrual capacity, small patient numbers mean that no concrete conclusions can be drawn from these data. In order to maximize patient safety, only centers with three or more inclusions in the DRAGON 1 trial, or with DRAGON Registry verified experience in PVE/HVE and a high accrual capacity, are eligible for participation in the DRAGON 2 randomized controlled trial (RCT).

All patients	PVE/HVE
Volumetry baseline	**N = 94/96[a]**
FLR volume at baseline in mL, median (IQR) (range)	364 (277–456) (154–971)
sFLR% at baseline, median (IQR) (range)	23·5 (19·4–27·5) (9·6–43·2)
sFLR <20% at baseline, n (%)	25 (27)
Volumetry week 1 post-embolization	**N = 84/96[a]**
FLR volume in mL, median (IQR) (range)	500 (424–621) (157–1084)
sFLR%, median (IQR) (range)	32·7 (27·3–38·4) (9·8–63·3)
Degree of hypertrophy (%) week 1, median (IQR) (range)	8·3 (4·3–12·4) (−3·9 to 37·8)
Volumetry week 3 post-embolization	**N = 60/70[a]**
FLR volume in mL, median (IQR) (range)	583 (476–678) (252–1433)
sFLR%, median (IQR) (range)	34·1 (29·7–39·5) (17·0–70·5)
Degree of hypertrophy (%) week 3, median (IQR) (range)	4·2 (1·3–7·2) (−4·2 to 38·7)
Kinetic growth rate (sFLR%/week) week 1–3, median (IQR) (range)	2·1 (0·7–3·6) (−2·1 to 19·3)
Volumetry week 6 post-embolization	**N = 20/24[a]**
FLR volume in mL, median (IQR) (range)	607 (497–732) (421–916)
sFLR%, median (IQR) (range)	35·3 (31·1–42·4) (23·3–57·2)
Degree of hypertrophy (%) week 6, median (IQR) (range)	4·3 (−0·6 to 9·0) (−6·6 to 12·2)
Kinetic growth rate (sFLR%/week) week 3–6, median (IQR) (range)	1·4 (−0·2 to 3·0) (−2·2 to 4·1)

FLR: future liver remnant; sFLR: standardized FLR; IQR; interquartile range. [a]x/y; x: number of patients where CT scan was performed; y: number of patients not yet planned for resection at the specific follow-up moment.

Table 3: **Volumetric measurements.**

Although parenchymal-sparing approaches to reduce perioperative risk are currently performed in most HPB units, this cohort was comprised of patients with extensive upfront unresectable CRLM, deemed ineligible for PSS by local multidisciplinary teams and requiring major anatomical resections to achieve complete metastasis clearance. The observed mortality rate should therefore be contextualized within the specific challenges of this selected and high-risk patient group. The DRAGON 2 RCT is needed to provide more insight into 90-day mortality in patients undergoing resection after PVE/HVE compared to post-resection 90-day mortality after PVE alone.

PHLF Grade B or C occurred in 22% of resected patients and was the cause of mortality in 86% of the deceased patients, despite collaborative consensus to use generally accepted FLR volume cut-offs for patients to undergo resection. In one of the deceased patients, resection was performed with a relatively small sFLR volume, especially considering multiple cycles of chemotherapy. In another case, resection was performed relatively early, i.e., within two weeks after PVE/HVE. Additionally, two more patients had a low sFLR or KGR and still underwent resection within three weeks after embolization. Generally, it was observed that most MDTs accepted an FLR volume cutoff of 30% to proceed to resection, even in patients with chemotherapy-damaged livers. The occurrence of PHLF and consequent mortality in this prospective patient series

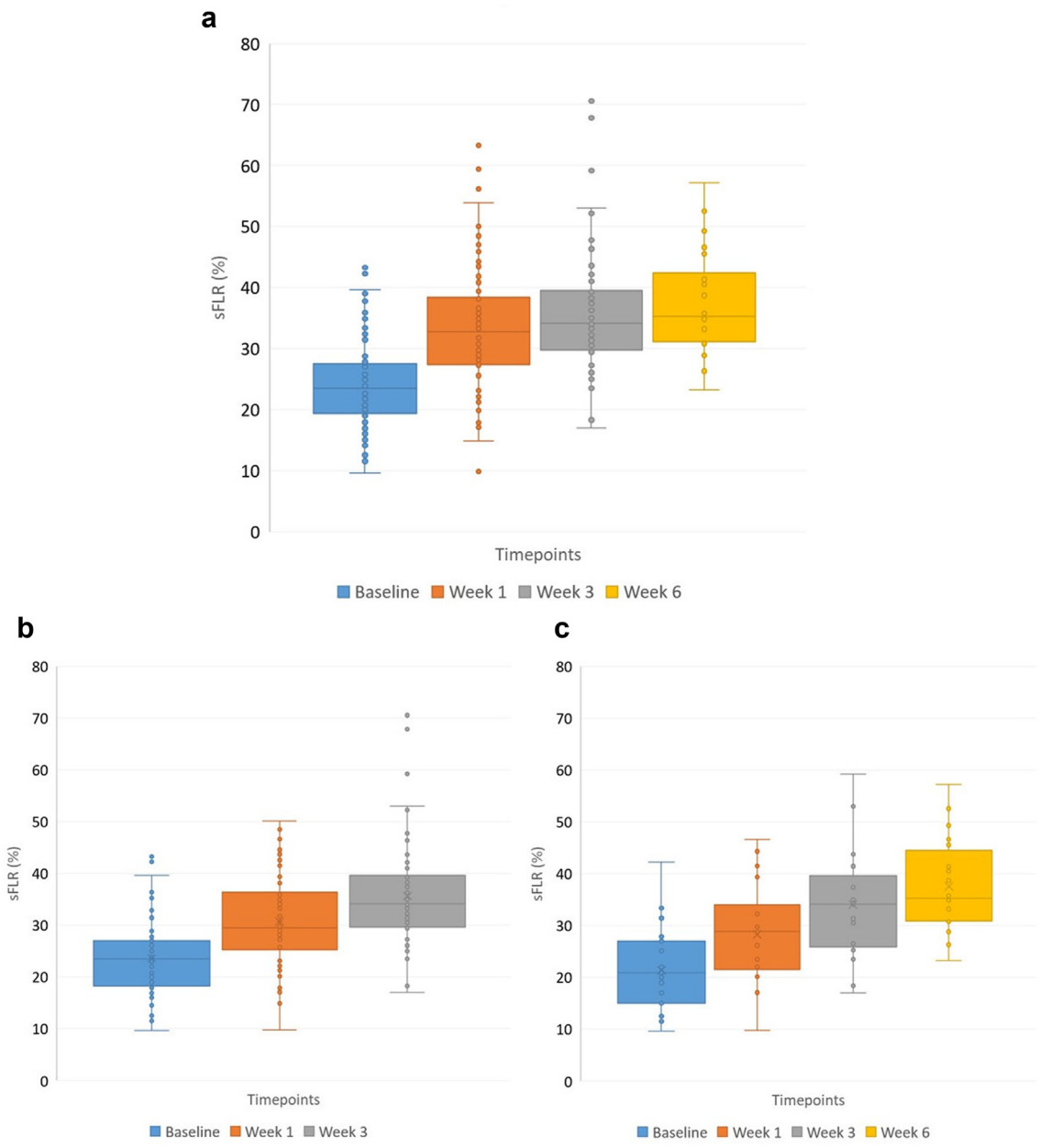

Fig. 2: Volume kinetics. Footnote: Changes in standardized FLR (sFLR%) after combined portal and hepatic vein embolization (PVE/HVE). a. Volume kinetics of all 96 patients that underwent PVE/HVE; b. Volume kinetics of the 70 remaining patients not yet planned for resection at week 3, the 26 patients that were planned for resection after week 1 are excluded; c. Volume kinetics of the 24 remaining patients not yet planned for resection at week 6, the additional 46 patients that were planned for resection after week 3 are also excluded.

suggests that FLR volume alone is not enough to determine safe resectability, or that a 30% FLR volume cutoff is too liberal and introduces an underestimated safety risk with high mortality. For low mortality, the FLR cutoff in damaged livers may be over 40% as suggested in an analysis for perihilar cholangiocarcinoma.[29] To determine an adequate FLR for safe resection, segmental liver function assessments, such as 99 mTc-mebrofenin hepatobiliary scintigraphy, is probably the only safe strategy, especially for patients after neoadjuvant systemic therapy.[8,30,31] The use of a KGR cutoff as suggested by the MD Anderson group for PVE (2% per week), may also be a valuable addition to improve the safety of extended liver resection, especially after PVE or PVE/HVE.[7]

In preparation for the randomized DRAGON 2 trial, accrual was assessed in the composite primary outcome as a prerequisite for center participation. Only half of participating centers succeeded in accruing a minimum of three patients over the course of the 2·5-year accrual

period and 14% of centers had zero inclusions. An important reason for slow or non-accrual was the prohibition of clinical trials in many participating hospitals during the COVID-19 pandemic. However, for many of the centers, it was not the number of eligible patients that limited accrual, but difficulties in effectively organizing patient inclusion and data management.

Regarding efficacy, PVE/HVE achieved a significant KGR and FLR hypertrophy, surpassing that of PVE alone but not reaching the levels observed with the ALPPS procedure. Specifically, one week after PVE/HVE, a KGR of 8·3%/week was observed, compared to 6·1% after PVE alone and 14·1% after ALPPS, as reported in the LIGRO trial.[2] Moreover, the observed resection rate after PVE/HVE is notably higher than the 75% after PVE alone and remains comparable to the 92% observed in ALPPS.[9,10] This high feasibility makes PVE/HVE an attractive procedure, since it avoids the need for two invasive operations like in ALPPS, replacing the first stage by a percutaneous intervention.

The hypertrophy and KGR observed in this study align with previously published data on LVD and PVE/HVE procedures.[12,14,32–34] However, it should be noted that the median growth rate three weeks after embolization may be underestimated, as 26 patients were already scheduled for resection and, therefore, did not undergo a CT scan at that time.

The high resection rate after PVE/HVE, seemingly due to more accelerated FLR growth compared to PVE alone, may improve long-term survival, quality of life, and cost-efficiency, as previously suggested in the retrospective multicenter DRAGON 0 cohort, published earlier by the DRAGON collaborative.[13] How this directly compares to PVE must be further assessed in a randomized trial.

This study presents certain limitations inherent to a single-arm design. First, while strenuous efforts were made to minimize selection bias, the presence of such bias is an intrinsic limitation in non-randomized trials. Second, FLR volume cut-offs and decision to move ahead with resection were left to participating centers. Strict volume cut-offs were intentionally not enforced, which adds an operator bias regarding the procedure: it may be that in some cases, resection was not timed appropriately. Volumetry was performed by local radiologists at the participating centers and was not repeated by the coordinating study team, making it more prone to inter-observer variability. Third, the lack of standardized segmental liver function assessments is a limitation of the trial. Hepatobiliary scintigraphy is the most promising method to standardize in the work-up for major liver resection; however, it is currently rarely implemented in clinical practice worldwide. Fourth, the study was limited to CRLM patients and the findings can therefore not be applied to patients with primary liver tumors. To address this shortcoming, the Dragon Trials Collaborative initiated the Dragon Registry and a randomized controlled trial comparing PVE and PVE/HVE in patients with primary liver cancers. This DRAGON primary liver cancer RCT expects to open early 2025 and is funded by the Dutch Cancer Society and Netherlands & Belgium Organizations for Health Research and Development.

Lastly, the trial revealed the challenges of international multicenter clinical trials with limited funding to accrue patients and to prospectively collect clinical data at predefined timepoints. Collaboration among study collaboratives and international governmental and non-governmental funding bodies must be strengthened to

All patients	PVE/HVE
	96
FLR volume before decision to resect in mL, median (IQR) (range)	586 (464–700) (288–1433)
sFLR%, before decision to resect, median (IQR) (range)	35·9 (30·8–41·6) (20·9–70·5)
Resection rate, n (%)	86 (90)
No resection, n (%)	10 (10)
Insufficient liver growth	1 (10)
Progression of disease on imaging	5 (50)
Progression of disease during surgical exploration	2 (20)
Post-embolization complications	1 (10)
Complete tumor response after chemotherapy	1 (10)
Resected patients	**86**
Time in days between intervention and resection, median (IQR) (range)	31 (24–52) (10–192)
Type of resection, n (%)	
Right hepatectomy	39 (46)
Extended right hepatectomy	45 (52)
Left hepatectomy	1 (1)
Extended left hepatectomy	1 (1)
Laparoscopic resection, n (%)	8 (9)
Operation time in minutes, median (IQR) (range)	240 (191–315) (75–475)
Blood loss in mL, median (IQR) (range)	583 (300–1000) (0–4500)
Post-operative hospital stay (days), median (IQR) (range)	7 (5–11) (0–137)
Negative resection margin, R0, n (%)	61 (72)
Bilirubin at POD 5 in mg/dL, median (IQR) (range)	1·22 (0·88–2·02) (0·16–13·9)
INR at POD 5, median (IQR) (range)	1·2 (1·1–1·3) (0·9–2·2)
Patients who met 50/50 criteria, n (%)	1 (1)
Patients with postoperative peak bilirubin >7 mg/dL, n (%)	8 (10)
Any complication, n (%)	49 (57)
Any major complication (≥ Grade 3), n (%)	30 (35)
Any liver-specific complication, n (%)	25 (30)
All liver-specific complications (≥ Grade 3), n (%)	27
Post hepatectomy liver failure	8 (9)
Bile leakage	13 (15)
Liver abscess	4 (5)
Ascites	8 (9)
Infected ascites and bacteremia	1 (1)
Liver hemorrhage	2 (2)
90-day postoperative mortality, n (%)	7 (8)

FLR: future liver remnant; sFLR: standardized FLR; IQR; interquartile range; R0: negative resection margin; POD: postoperative day; INR: international normalized ratio. Complications defined according to Clavien-Dindo classification.

Table 4: **Surgical outcomes.**

improve the chance of success for large international trials.

This prospective multinational study demonstrates that PVE/HVE is safe, without embolization-related mortality, and results in a high resection rate in patients with upfront unresectable colorectal liver metastases. The lower than anticipated accrual potential of centers was a result of the COVID pandemic inclusion stops and limited funding of participating centers. Despite the FLR augmentation strategy, morbidity and mortality after resection remained higher than desired and largely coincided with PHLF. This may be explained by a lack of information on true functional capacity of the FLR. The randomized controlled DRAGON 2 trial, currently recruiting, aims to further assess the role and long-term outcomes of PVE and PVE/HVE in patients with CRLM.

Contributors

All authors contributed to the study design, data collection, and writing—review & editing. Specific contributions were as follows: R. Korenblik, S. James, J. Smits: Study design, literature search, figures, data collection, data analysis, data interpretation, writing—original draft, project administration, funding acquisition. E. Schadde, C.A. Binkert, M.H.A. Bemelmans: Study design, data collection, data interpretation, writing—review & editing, project administration, supervision, funding acquisition. R.M. van Dam, C. van der Leij, M. Dewulf: Study design, literature search, figures, data collection, data analysis, data interpretation, writing—original draft, project administration, supervision, funding acquisition.

Data sharing statement

R. Korenblik, S. James, J. Smits, C. van der Leij, M. Dewulf, and R.M. van Dam had full access to all study data and take responsibility for data integrity and accuracy. Data supporting the findings of this study are available from the corresponding author upon reasonable request, after proposal approval and a signed data sharing agreement.

Declaration of interests

C.A. Binkert: research support from Abbott Laboratories; consulting fees from CTI Vascular, Biotronic (consulting on technology). Å.A. Fretland: honoraria from Bayer, Angiodynamics, Medtronic (speaker). D.C. Madoff: Receipt of equipment from Abbott Laboratories (plugs), Guerbet (lipiodol), Boston Scientific (embolic particles) for pre-clinical animal studies; consulting fees from Guerbet, Boston Scientific (advisory board). G. Martel: unrelated research grants from Canadian Institutes of Health Research, Canadian Blood Services. R.M. van Dam: research grants and study materials from Abbott Laboratories, Guerbet.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2025.101284.

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