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INTERVENTIONAL

Can cone-beam CT tumor blood volume predicts the response to chemoembolization of colorectal liver metastases? Results of an observational study

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Abstract

Purpose To determine whether intraprocedural C-arm cone-beam CT (CBCT) parenchymal blood volume (PBV) can predict the response of colorectal cancer liver metastases (CRCLM) 2 months after irinotecan drug–eluting bead (DEBIRI) chemoembolization.

Materials and methods This single-center observational study was compliant with the Helsinki Declaration and approved by our institutional review board. Thirty-four consecutive CRCLM patients referred for DEBIRI chemoembolization were enrolled between March 2015 and December 2016. Tumor size was assessed at baseline and 2 months after DEBIRI chemoembolization by multidetector CT (Response Evaluation Criteria in Solid Tumors RECIST 1.0), and PBV was measured before and after DEBIRI chemoembolization. Two independent readers reviewed all data. We determined the potential correlation (Spearman's rank correlation) between intraprocedural PBV values and tumor response at 2 months. The relationship between tumor response and PBV was studied using a mixed model. A logistic regression model was applied to study the relationship between patient "Responder/Non-responder" and PBV.

Results There was a strong correlation between baseline PBV or the percent change of PBV and the 2-month tumor response (rho = −0.8587 ($p = 0.00001$) and rho = 0.8027 ($p = 0.00001$), respectively). The mixed model showed that an increase of 1 ml/1000 ml in PBV of a tumor before DEBIRI chemoembolization led to a 0.54 mm decrease in diameter ($p < 0.005$). A 1% decrease in PBV after DEBIRI chemoembolization resulted in tumor shrinkage of 0.75 mm ($p < 0.005$). The logistic regression model showed that patients with a 1% smaller mean decrease of PBV after DEBIRI chemoembolization had a 10% lower likelihood of achieving disease control (OR = 0.9, 95% confidence interval (CI) = 0.81–1; $p = 0.0493$).

Conclusion Intraprocedural PBV may predict tumor response to DEBIRI chemoembolization.

Key Points

- *There is a strong relationship between the parenchymal blood volume (PBV) of colorectal liver metastases before DEBIRI chemoembolization and tumor response at 2 months.*
- *Higher PBV values before DEBIRI chemoembolization correlate with greater tumor shrinkage, but only if the PBV decreases by more than 70% after DEBIRI chemoembolization.*
- *Each increase of 1% in the mean decrease of PBV after DEBIRI chemoembolization resulted in a 10% lower likelihood of achieving disease control (OR = 0.9, 95% confidence interval (CI) = 0.81–1; p = 0.0493).*

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Keywords Therapeutic chemoembolization · Liver neoplasms · Cone-beam computed tomography · Multidetector computed tomography · Perfusion imaging

Abbreviations

CBCT	Cone-beam computed tomography
CR	Complete response
CRCLM	Colorectal cancer liver metastases
DEBIRI	Irinotecan drug–eluting bead
ICC	Intraclass correlation coefficient
MDCT	Multidetector computed tomography
PBV	Parenchymal blood volume
PD	Progressive disease
PR	Partial response
RECIST 1.0	Response Evaluation Criteria in Solid Tumors 1.0
ROI	Region of interest
SD	Stable disease
TACE	Transarterial chemoembolization

Introduction

Liver metastases are the leading cause of death of patients with colorectal cancer. They occur in 50–75% of patients during the course of the disease, but only 10–15% are suitable for surgical removal [1]. Systemic chemotherapy can improve long-term survival by increasing the resectability of liver metastases to 20% of patients, increasing the median overall survival to 3.5 years [2]. However, systemic chemotherapy often fails to downstage enough metastases to allow surgical resection and relapses are frequent. In these cases, systemic treatment may have only a limited effect, and the results of current strategies are often disappointing, particularly for KRAS-mutated patients who cannot receive anti-EGFR therapies. Irinotecan drug–eluting bead (DEBIRI) chemoembolization has been developed as a local treatment for colorectal cancer liver metastases (CRCLM) [3, 4]. Localized and controlled drug release, combined with embolization, improves localized cytotoxicity with a 93% disease control rate and 8 months of liver progression-free survival and 13 months of overall survival [5].

There is no imaging endpoint to indicate the success of transarterial chemoembolization (TACE) in CRCLM, in contrast to hepatocellular carcinoma (HCC), in which the complete disappearance of tumor enhancement on final dual-phase C-arm cone-beam CT (CBCT) is linked to success [6]. Completion of TACE in CRCLM is based only on the complete injection of irinotecan drug–eluting beads into each liver lobe. Treatment outcomes can only be assessed at the 2-month imaging follow-up [7]. There is thus a clear need for a preoperative surrogate biomarker that can predict treatment success/failure.

Parenchymal blood volume (PBV), assessed by C-arm CBCT, is a quantitative parameter to assess tumor perfusion. There is a strong correlation between PBV and CT perfusion in HCC tumors (rho = 0.0903; $p < 0.001$) [8].

The goal of our study was to determine whether the pre-/post-chemoembolization PBV correlates with the 2-month tumor response rate and whether it can be used to predict the tumor and liver response of CRCLM patients 2 months after treatment with DEBIRI chemoembolization.

Materials and methods

Study cohort

This was a fully compliant, single-institution, observational study, approved by the hospital institutional review board. Patients enrolled in the study were referred for DEBIRI chemoembolization for CRCLM after failure of oxaliplatin- and irinotecan-based chemotherapies. Patients were considered to be eligible for DEBIRI chemoembolization based on the clinical indications and contraindications shown in Table 1.

Table 1 Clinical indications and contraindications for patient selection for DEBIRI chemoembolization

Clinical indication:
Pathologically proven colorectal cancer
Evidence of bilobar CRCLM involvement by CT scan
Progressive disease (PD) in the liver at the time of inclusion
Oxaliplatin- and irinotecan-based chemotherapy failures
Non-resectable liver metastases
< 4 stable extrahepatic lesions
ECOG-PS < 2
Adequate hematological function (neutrophil ≥ 1.0 × g/l, platelets ≥ 75 × g/l)
Adequate liver function (Child-Pugh classification A or B)
Total bilirubin ≤ 20 μmol/l
Albumin ≥ 25 g/l
Adequate renal function (creatinine < 200 μmol/l)
Life expectancy of more than 12 weeks
Clinical contraindication:
Portal vein thrombosis/invasion or portal vein hypertension
Any contraindication for hepatic embolization portosystemic shunt; biliary duct dilatation)
Transaminase levels ≥ 5 times the upper limit of normal or > 250 UI/l
Severe allergy to iodinate contrast media

Multidetector computed tomography acquisition

All patients underwent liver multidetector computed tomography (MDCT) at baseline and 2 months after chemoembolization. A Siemens Somatom 128 detector CT unit (Siemens Healthcare) with a biphasic imaging protocol was used. Non-enhanced and enhanced contrasts at the portal phase images were acquired at a 0.625 mm slice thickness reconstructed to 3 mm. Table 2 summarizes the image modality acquisition parameters.

DEBIRI chemoembolization

All chemoembolization procedures were performed as described by Lencioni et al. [9]. After selective catheterization of the right and left hepatic arteries using a microcatheter, each liver lobe was treated with 3 ml DC Bead™ M1 (70–150 μm; BTG) loaded with 100 mg irinotecan. Both lobes were treated in the same session, and no additional embolization was performed.

C-arm CBCT acquisition

Intraprocedural images were acquired using a flat panel angiographic system (Artis Q Pure, Siemens Healthcare).

PBV acquisition consisted of two consecutive spins. A first spin (mask run) without contrast enhancement was followed 7 s later by a second spin after contrast medium injection (fill run). Both spins ran during a single breath hold (17 s). Contrast media were injected into the proper hepatic artery through a 2.7-Fr microcatheter (Progreat™ Terumo) using a power injector (Arterion®, Medrad, Inc.®) 7 s before the acquisition of the second rotation. Twelve milliliters of iobitridol (Xenetix 350®, Guerbet) mixed with 24 ml saline solution was injected at 3 ml/s. Table 2 summarizes the image modality acquisition parameters.

PBV calculation

A Syngo workstation (Siemens Healthcare) with a PBV application was used to post-process C-arm CBCT images. PBV is an

Table 2 Image modality acquisition parameters

	MDCT	C-arm CBCT
System	Siemens Somatom Definition AS$^+$ 128-slice Siemens Healthcare	Artis Q Pure; Siemens Healthcare
Acquisitions parameters		C-arm rotation = 200° clockwise arc
	Scan time = 15 s	248 projection images (30 frames/s)
	Field of view = 140 × 60	Scan time = 5 s
	Scan length = 480 mm	Field of view = 30 × 40 cm
	Rotation time = 0.5 s	Reconstruction algorithm: Feldkamp back
	Slice thickness = 0.6 mm	Voxel size = 0.5 mm^3 isotropic
	Slice reconstruction = 3 mm	Slice thickness = 1 mm
	Collimation = 128 × 0.6 mm	Slice reconstruction = 3 mm
	Matrix = 512 × 512	Matrix 616 × 480
Tube settings	Kv = 120	Kv = 90
	Effective mAs = 170	Effective mA = 300
Acquisitions protocol	Triphasic	PBV
	Unenhanced	Unenhanced triggered at 1 s
	Portal phase triggered at 70 s	Steady-state phase triggered at 7 s
Injection protocol	Q = 3 ml/s	Q = 3 ml/s
	V = 100 ml	V = 36 ml (12 ml iobitridol + 24 ml saline mix)
	PSI = 800	PSI = 300
	Injection site: antecubital vein	Injection site: proper hepatic artery
Power injector used	Medrad® Stellant® (Bayer HealthCare)	Medrad® Mark 7 Arterion® (Bayer HealthCare)
Contrast media used	Iobitridol, 350 mg I/ml (Guerbet)	Iobitridol, 350 mg I/ml (Guerbet)

application that enables determination of the parenchymal blood volume at steady-state contrast enhancement [10]. The mask and fill volumes were registered with a non-rigid motion correction algorithm and then subtracted. To allow the calculation of the arterial input function, the hepatic artery was segmented from the liver parenchyma and then the arterial input function value was calculated from an automated histogram analysis of the vessel tree. The arterial input function value was then applied as a scaling factor to obtain the quantitative parenchymal blood volume map. A smoothing filter was applied to reduce pixel noise. The blood volume pixel value is presented to the reader in a parametric color-coded image that allows direct parenchymal blood volume calculation.

Image analysis

The study coordinator retrieved and anonymized all MDCT images and PBV image batches on the Syngo workstation from our PACS. Five representative lesions per patient were labeled in both image modalities. Two readers independently interpreted the images.

Each reader determined the size of the five labeled hepatic lesions from the MDCT image, according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 [11], at baseline and 2 months. A week later, the pre- and post-chemoembolization PBV batches were separately presented to both readers. They drew a region of interest (ROI), covering only the tumor (avoiding normal liver tissues) for all five labeled tumors per patient, and reported the tumor blood volume value in ml of blood/1000 ml of tissue.

Statistics

Statistical analysis was performed with SAS software (version 9.4, SAS Institute). Results are presented as the mean ± standard deviation (SD). A p value of < 0.05 indicates a statistically significant difference. The interobserver agreement of tumor size based on MDCT and PBV images was determined using the intraclass correlation coefficient (ICC) as described by Shrout and Fleiss [12]. Intraclass correlation values were classified as follows: ICC < 0.40, poor agreement; ICC from 0.40 to 0.60, moderate agreement; ICC from 0.60 to 0.80, substantial agreement; and ICC > 0.80, good agreement [12].

The correlation between baseline tumor PBV values before and after chemoembolization, as well as the change of PBV, and the tumor response at 2 months was determined using Spearman's rank correlation coefficient. We classified the tumors by quartile according to their initial blood volume value to stratify the behavior of the CRCLM. The relationship between the change in tumor size, pre-DEBIRI chemoembolization tumor blood volume, and percent change of PBV after DEBIRI chemoembolization was also assessed using a mixed model considering the individual deviations (several lesions per patient).

The relationship between the variable "Responder/Non-responder" and the tumor blood volume was assessed using a logistic regression model. Patients were considered to be "Responders" if the RECIST 1.0 status was complete response (CR), partial response (PR), or stable disease (SD) and "Non-responders" if the RECIST 1.0 status was progressive disease (PD).

Results

Patient demographics

Forty-five CRCLM patients were screened at our multidisciplinary liver tumor board for intra-arterial therapy between March 2015 and December 2016 (Fig. 1). Thirty-four patients (19 men) with a mean age of 63 years ± 10 years [range 43; 80] underwent DEBIRI chemoembolization for CRCLM and PBV measurements. All patients had multiple liver lesions of PD status (RECIST 1.0) at inclusion. The nine excluded patients were treated with radio-embolization ($n = 2$) or hepatic intra-arterial chemotherapy ($n = 7$). Two further patients were excluded because they did not complete the entire PBV protocol because of painful administration of the DEBIRI chemoembolization. All the 34 patients had a modal liver arterial supply.

Patients had previously undergone a median of three [2–6] chemotherapy lines. No patients had previously undergone liver surgery and/or percutaneous ablation. The ECOG-PS was 0 for 28 patients (82%) and 1 for six (18%). The mean indwelling time between the baseline MDCT and the DEBIRI chemoembolization was 17 days ± 3.2 days (13–25). The mean size of the target tumors was 35 mm ± 23 mm [range 11; 191] at baseline, accounting for a mean baseline RECIST 1.0 sum of 174 mm ± 66 mm [range 92; 380] per patient (Table 3).

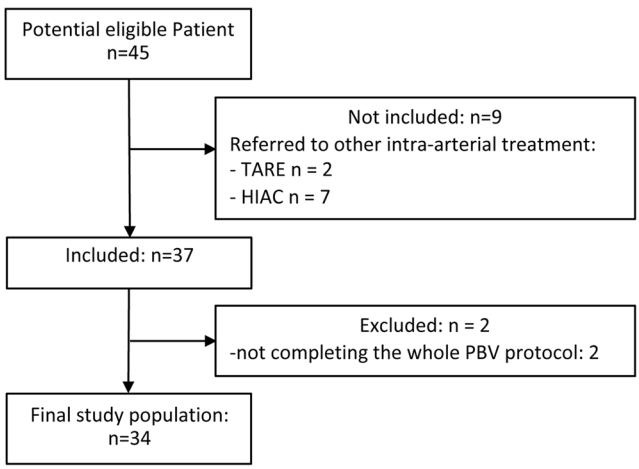

Fig. 1 Patient flow chart

All 34 patients successfully completed both pre- and post-chemoembolization PBV acquisition. A total of 276 CRCLM were seen in the 34 patients. Thus, this is accounting for a mean number of MCRCLM per patient of 8.1 ± 2.9 (5–14). Both readers correctly identified all 170 target lesions.

Tumor and patient response rates according to RECIST 1.0

The mean size of the target tumor was 29 mm ± 23 mm [range 0; 191], and the mean RECIST 1.0 sum was 147 mm ± 82 mm [range 60; 392] at the 2-month follow-up. The liver lesions were considered to be controlled for 30 patients (88%) (PR = 11 (32%), SD = 19 (56%)), and four (12%) had progressive disease. The mean RECIST 1.0 tumor response rate was 13% ± 26% [range − 65; 49] (Table 3). There was excellent agreement between the two readers (ICC > 0.74; $p < 0.001$).

PBV and prediction of tumor response

PBV measurement

The mean PBV value of all CRCLM target lesions was 62 ml ± 47 ml/1000 ml [range 10; 195] and 17 ml ± 8 ml/1000 ml [1; 59] ($p < 0.0001$) before and after chemoembolization, respectively. This accounts for an average reduction of PBV of 55% ± 29% [range − 99; 0]. Figure 2a–d shows a representative case.

Correlation between PBV and tumor size

There was a strong correlation between PBV before chemoembolization and the reduction of tumor diameter at 2 months (rho = − 0.8587; $p = 0.00001$), as well as between the percent change of PBV after DEBIRI chemoembolization (rho = 0.8027; $p = 0.00001$) and reduction of tumor diameter (Spearman's rank correlation). In addition, there was a moderate correlation between post-chemoembolization PBV and reduction in tumor diameter (rho = − 0.4553; $p = 0.00001$).

Tumor classification according to their initial PBV resulted in 44 tumors in group 1 (initial PBV < 20 ml/1000 ml), 41 tumors in group 2 (initial PBV of 20 ml/1000 ml to 50 ml/1000 ml), 43 tumors in group 3 (initial PBV of 51 ml/1000 ml to 100 ml/1000 ml), and 42 tumors in group 4 (initial PBV > 100 ml/1000 ml) (Table 4). For group 4, DEBIRI chemoembolization resulted in a 51% reduction of tumor diameter and an 84% decrease in PBV, with a moderate correlation between the reduction in tumor diameter and that of PBV (rho = − 0.5469; $p = 0.00018$). The equivalent values for the other groups following DEBIRI chemoembolization treatment were as follows: a 24% reduction in tumor diameter and a 70% decrease in PBV for group 3, with a moderate correlation between the reduction in diameter and that of PBV (rho = − 0.4871; $p = 0.00093$); a 1% increase in tumor diameter and a 51% decrease of PBV for group 2, with a moderate correlation between the reduction in diameter and that of PBV (rho = 0.0290; $p = 0.85695$); and a 23% increase in tumor diameter and a 15% decrease in PBV for group 1, with a moderate correlation between the reduction in diameter and that of PBV (rho = − 0.4046; $p = 0.00645$).

Prediction of tumor shrinkage

We assessed the relationship between the change in tumor size and PBV using a mixed model, considering the individual deviations (several lesions per patient). Each increase of 1 ml/1000 ml in tumor blood volume of the tumor before DEBIRI chemoembolization was associated with a decrease of 0.54 mm in tumor diameter at the 2-month follow-up ($p < 0.005$). In addition, each 1% decrease in tumor blood volume after DEBIRI chemoembolization was associated with a decrease of 0.75 mm in tumor diameter at the 2-month follow-up ($p < 0.005$).

Quartile analysis using the mixed model showed that each decrease of 1% in tumor blood volume after DEBIRI chemoembolization was associated with a 7 mm decrease in tumor diameter at the 2-month follow-up ($p < 0.005$) for tumors with a PBV > 100 ml/1000 ml before DEBIRI

Table 3 Changes in tumor size and PBV values before and after chemoembolization

Feature	Before chemoembolization	After chemoembolization	% change after chemoembolization	*p* value
Per tumor ($n = 170$)				
Tumor size (mm)	35 ± 23 [11; 191]	29 ± 23 [0; 191]	− 13 ± 34 [− 100; + 85]	< 0.0001
PBV (ml/1000 ml)	62 ± 47 [10; 195]	17 ± 8 [1; 59]	− 55 ± 29 [− 99; 0]	< 0.0001
Per patient ($n = 34$)				
RECIST 1.0 sum* (mm)	174 ± 66 [92; 380]	147 ± 82 [60–392]	− 13 ± 26 [− 66; 49]	< 0.0001
PBV (ml/1000 ml)	62 ± 38 [13; 141]	17 ± 5 [10–31]	− 55 ± 22 [− 90; 0]	< 0.0001

Values are presented as the mean ± standard deviation [min; max]

*Two months after DEBIRI chemoembolization

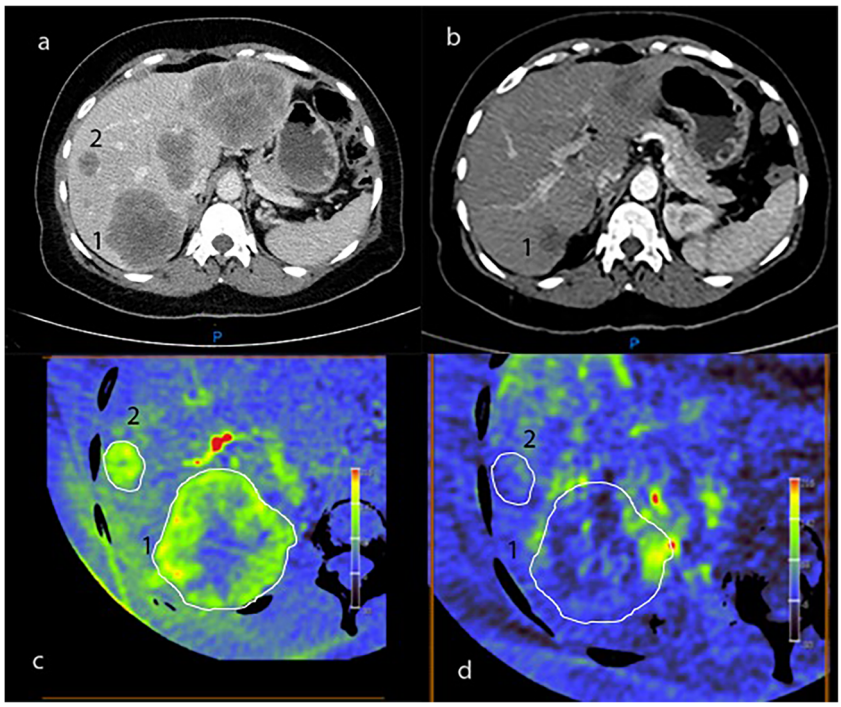

Fig. 2 Representative case of a 68-year-old man with CRCLM referred for DEBIRI chemoembolization. Two of five index lesions are shown. Lesion 1 (71 mm on baseline MDCT (**a**)) had an initial PBV of 181 ml/1000 ml (**c**) that dropped to 32 ml/100 ml after DEBIRI chemoembolization (**d**). This lesion had partial response at the 2-month MDCT follow-up (20 mm (**b**)). Lesion 2 (20 mm on baseline MDCT (**a**)) had an initial PBV of 149 ml/1000 ml (**c**) that dropped to 18 ml/100 ml after DEBIRI chemoembolization (**d**). This lesion had complete response at the 2-month MDCT follow-up (**b**)

chemoembolization (group 4). The corresponding values for tumors of the other groups were the following: group 3, a 2 mm decrease in tumor diameter for each 1% decrease in tumor blood volume ($p < 0.005$); group 2, a 1 mm decrease in tumor diameter for each 1% decrease in tumor blood volume ($p < 0.005$); and group 1, a 2 mm increase in tumor diameter for each 1% decrease in tumor blood volume ($p < 0.005$).

Prediction of patient response according RECIST 1.0

Patients with a 1% smaller mean decrease of PBV after DEBIRI chemoembolization had a 10% lower likelihood of achieving disease control (OR = 0.9, 95% confidence interval (CI) = 0.81–1; $p = 0.0493$). Table 5 shows the results of the logistic regression model to estimate the odds and likelihood of disease control as a function of predictors: pre-DEBIRI

Table 4 Changes in tumor size and PBV values before and after chemoembolization by group (per tumor analysis)

	Group 1 Pre-DEBIRI chemoembolization PBV (< 20 ml/1000 ml, $N = 44$)	Group 2 Pre-DEBIRI chemoembolization PBV (20–50 ml/1000 ml, $N = 41$)	Group 3 Pre-DEBIRI chemoembolization PBV (51–100 ml/1000 ml, $N = 43$)	Group 4 Pre-DEBIRI chemoembolization PBV (> 100 ml/1000 ml, $N = 42$)
MDCT tumor size				
Baseline tumor size (mm)	28 ± 16 [18; 33]	38 ± 33 [21; 43]	32 ± 15 [21; 42]	42 ± 23 [28; 44]
2-month tumor size (mm)	34 ± 23 [18; 43]	38 ± 34 [21; 45]	24 ± 14 [14; 31]	21 ± 17 [12; 24]
2-month % change in tumor size	+ 23 ± 30 [− 6; + 44]	+ 1 ± 18 [− 7; + 6]	− 24 ± 19 [− 35.5; − 18]	− 51 ± 17 [− 60; − 39]
PBV value				
Pre-DEBIRI chemoembolization PBV (ml/1000 ml)	13 ± 4 [10; 15]	37 ± 9 [28; 44]	68 ± 10 [59; 75]	131 ± 30 [105; 151]
Post-DEBIRI chemoembolization PBV (ml/1000 ml)	11 ± 1 [10; 11]	17 ± 5 [13; 21]	20 ± 8 [14; 25]	21 ± 9.5 [15; 25]
Intraprocedural % PBV change	− 15 ± 15 [− 24; 0]	− 51 ± 17 [− 64; − 46]	− 70 ± 13 [− 78.5; − 62]	− 84 ± 7 [− 87; − 82]

Values are presented as the mean ± standard deviation [min; max]

chemoembolization PBV, post-DEBIRI chemoembolization PBV, and percent change of PBV after chemoembolization (Fig. 3).

Discussion

Our results show that PBV which represents tumor blood volume can be a predictor of tumor response to DEBIRI chemoembolization: the higher the PBV before DEBIRI chemoembolization, the more the tumor shrinks if the PBV decreases by more than 70%. However, the overall impact on the liver response rate was only modest based on RECIST 1.0, because not all CRCLM respond in the same way in the same patient.

The benefit between embolization and local delivery of irinotecan is not clearly established in terms of efficacy. One can speculate that the tumor response is mostly due to irinotecan as CRCLM are lesser hypervascular than HCC. However, the role of irinotecan stays controversial as irinotecan must be converting into its active metabolites (SN38) by normal hepatocytes [13]. In fact, we show that tumor response can occur if the tumor shows a blood volume > 100 ml/1000 ml before DEBIRI chemoembolization and if the decrease of the blood volume after DEBIRI chemoembolization is > 70%. These facts are in favor of a significant role of embolization even if quantification of irinotecan effect is not evaluable.

These results confirm PBV as a valuable surrogate biomarker of tumor response/failure to DEBIRI chemoembolization (Fig. 4).

In 2009, Zellerhoff et al. [10] described the use of C-arm CBCT for the evaluation of PBV. The calculation of PBV assumes that the contrast concentration in the imaged liver tumor is constant for the duration of a single C-arm CBCT acquisition, given adequate injection of the contrast solution. This leads to the calculation of the PBV when tumor enhancement reaches a steady state. The quantitative PBV values are given in ml/1000 ml [14–16]. PBV has mostly been evaluated for HCC and is considered as a highly reproducible method for parenchymal blood volume measurement [17].

Syha et al. [18] demonstrated the clinical utility of PBV for immediate post-treatment assessment of drug-eluting bead (DEB)-TACE in HCC patients. They showed that all treated

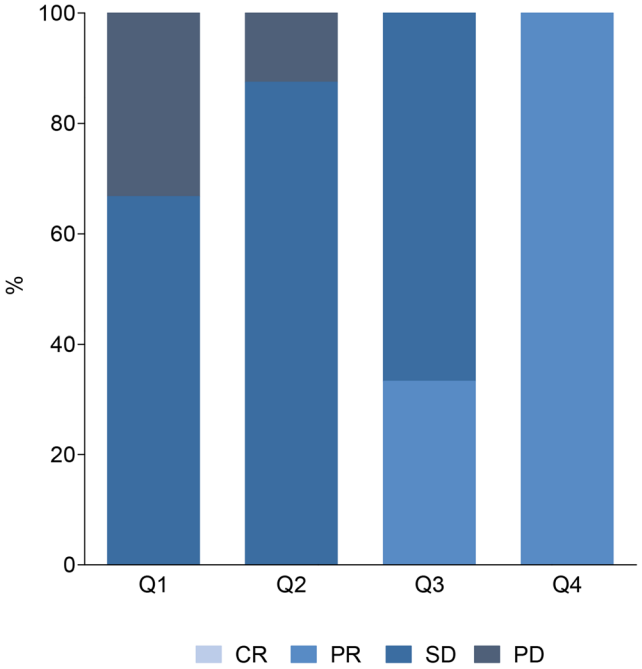

Fig. 3 Proportion of the RECIST 1.0 response (per patient) at 2 months by quartiles of parenchymal blood volume measured at baseline. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. Quartiles of parenchymal blood volume: Q1 < 20 ml/1000 ml, Q2 = 20–50 ml/1000 ml, Q3 = 51–100 ml/1000 ml, and Q4 > 100 ml/1000 ml

lesions exhibited a significant decrease in PBV after DEB-TACE (mean difference, − 15.61 ml/1000 ml; $p < 0.0001$). Less tumor shrinkage over time was observed for lesions exhibiting residual PBV (− 0.02 ± 0.49 vs. − 0.76 ± 0.38; $p < 0.0001$). Vogl et al. [19] studied PBV in a larger cohort of 111 patients, with a mixture of primary and secondary liver tumors, referred for DEB-TACE. They reported that the mean pre-DEB-TACE PBV for HCC, CRCLM, and breast cancer liver metastases were 98 ml/1000 ml, 64 ml/1000 ml, and 108 ml/1000 ml, respectively. They showed a correlation between initial PBV and the percent change of PBV after DEB-TACE (rho = 0.61; $p < 0.0001$), but it was not significant when analyzed tumor-by-tumor. They also reported that patients with an initial PBV > 100 ml/1000 ml showed 7.1% tumor shrinkage; those with a PBV of 50–100 ml/1000 ml, 4.6% tumor shrinkage; and those with a PBV < 50 ml/1000 ml, 2.8% tumor shrinkage. However, the authors failed

Table 5 Results of the logistic regression model used to predict the probability of disease control at 2 months as a function of covariates

Variable	Logistic regression		
	Odds ratio	95% Wald CI	*p* value
Pre-DEBIRI chemoembolization PBV	1.121	0.978; 1.284	0.1003
Post-DEBIRI chemoembolization PBV	5.765	0.619; 53.726	0.124
% change of PBV after DEBIRI chemoembolization	0.9	0.811; 1	0.0493

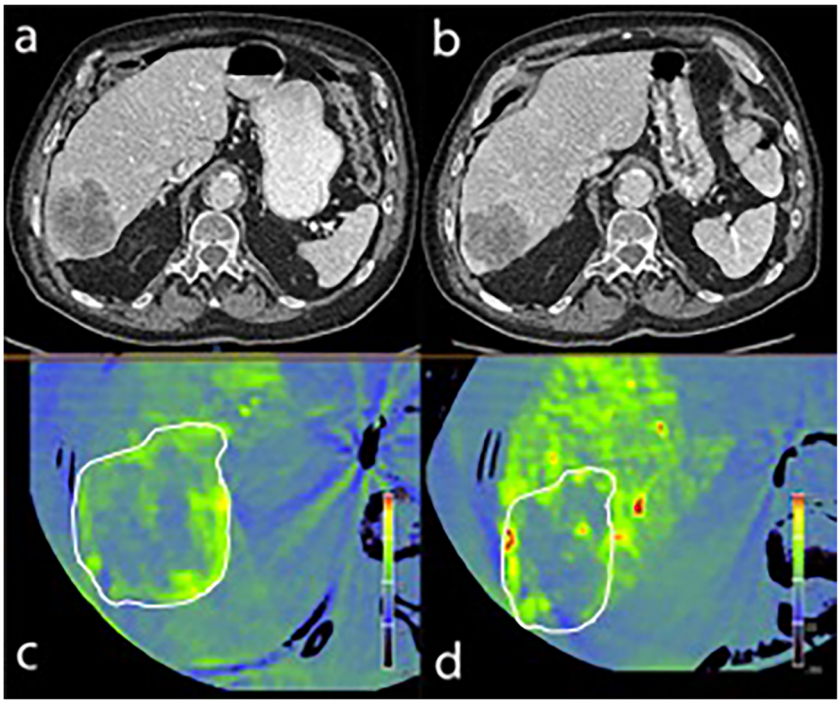

Fig. 4 Representative case of a 72-year-old woman with CRCLM referred for DEBIRI chemoembolization. One of five index lesions is shown. At baseline, the lesion size was 62 mm (**a**) with an initial PBV of 81 ml/1000 ml (**c**). After the chemoembolization, the PBV dropped to 45 ml/100 ml (**d**). This lesion had a 24% shrinkage at response at the 2-month MDCT follow-up (**b**), with the lesion size of 47 mm

to demonstrate a significant correlation between pre-DEB-TACE PBV or change of PBV and change in tumor size.

The choice of *the ideal* perfusion parameter to quantify perfusion change after chemoembolization is critical. Kaufmann et al. [20, 21] had screened different perfusion parameters (blood flow blood volume, arterial liver perfusion, hepatic perfusion index) to assess an early predictive factor of success of doxorubicin-eluting bead chemoembolization in a HCC patient cohort with a CT-based volume perfusion technique. They showed that early CT-based volume perfusion examination studying blood volume had a high accuracy that yielded a sensitivity of 76% and a specificity of 100% for the prediction of tumor response at 80 days.

The reliability of PBV was studied by Pereira et al. [22]. They compare the value of the tumor blood volume before and after chemoembolization in patients with melanoma liver metastases referred to drug-eluting bead chemoembolization with CBCT and MDCT modalities. Their results show that the change of tumor blood volume after chemoembolization had a similar proportion of variation between CBCT and MDCT, thus establishing a good reliability.

The dynamic contrast enhancement approach with CT or MRI reveals early changes within the CRCLM after intra-arterial therapies, such as transarterial radio-embolization (TARE). Reiner et al. [23] studied the value of arterial perfusion of CRCLM before and after TARE and compared the results to tumor response at 4 months. Arterial perfusion was defined as arterial blood flow (in ml/min/100 ml) in their study. They showed that responders had significantly higher arterial perfusion before TARE and exhibited a greater decrease in arterial perfusion after TARE. Conversely, non-responders had no significant reduction in arterial perfusion. The effect in responders was strong enough to influence 1-year overall survival, which was significantly higher for patients who showed a significant decrease in the arterial perfusion coefficient after TARE.

Boas et al. [24] showed that an arterial enhancement fraction (hepatic artery blood volume divided by the total blood volume) of less than 0.4 was associated with a 40% response rate using a less-sophisticated perfusion approach, whereas an arterial enhancement fraction of greater than 0.75 was associated with a 78% response rate for CRCLM treated with TACE. These results are in line with ours.

Early recognition of therapeutic failure is crucial to guide patient treatment decisions after chemoembolization, especially when other therapeutic options, such as percutaneous ablation (for lesions of < 3 cm) or hepatic intra-arterial chemotherapy are available. Ruers et al. [25] demonstrated in a phase II trial that iterative percutaneous ablation of CRCLM, when technically feasible, combined with chemotherapy in non-resectable patients was associated with better long-term overall survival than chemotherapy alone. Our work thus paves the way for a tumor-by-tumor approach, in which non-responders' tumors could be referred for early ablation without the need to wait to the 2-month follow-up and thus may have increasing tumor response.

Our study had several limitations. First, the patient sample was small, only including patients who were undergoing their first DEBIRI chemoembolization procedure. Findings in previously treated patients may have been different. Second, the

study coordinator chose only well-delineated lesions as target lesions, and those surrounded by streak artifacts from catheters or located in truncated liver segments were not considered for the study. Moreover, even if the lesions are well delineated, some non-evaluable quantity of normal liver may be accounted within the tumor. This may account for potential errors in the estimated tumor PBV, especially for small or non-circular lesions. Third, a broad heterogeneity of PBV value was observed at baseline; however, this heterogeneity had no significant impact on results as the PBV values were analyzed per quartile with an appropriate statistical method. Fourth, this technology is owned by Siemens Healthcare and is not available with other centers. Fifth, the optimum timing for assessing the CRCLM response after DEB-TACE is still unclear. We choose a 2-month follow-up to be between early (e.g., 1 month) and late (e.g., 4 months) evaluations. The shortest in-patient follow-up tends to underestimate the tumor response rate, whereas the late evaluation tends to miss the highest response or early progression. Finally, we do not yet have the long-term follow-up evaluation of patient outcomes and thus cannot claim that patients with better tumor responses have better clinical outcomes. The clinical significance of these findings must be validated in the future with a larger multicenter study. A longer follow-up is also required to determine whether tumor PBV can reliably help predict patient prognosis.

Our study suggests the utility of PBV as a surrogate biomarker to predict early success/failure of DEBIRI chemoembolization for treatment of CRCLM. PBV could be used to optimize treatment following DEBIRI chemoembolization through better individualization of treatment schedules.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Olivier Pellerin, Deputy Head of the Department of Interventional Radiology at Hôpital Européen Georges-Pompidou.

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

Statistics and biometry Hélena Pereira, PhD, and Prof. Gille Chatellier, MDE, PhD, both as co-authors, have significant statistical and methodology expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional review board approval was obtained.

Methodology
- prospective
- observational
- performed at one institution

References

1. de Baere T, Deschamps F (2011) Arterial therapies of colorectal cancer metastases to the liver. Abdom Imaging 36:661–670
2. Heinrich S, Lang H (2013) Liver metastases from colorectal cancer: technique of liver resection. J Surg Oncol 107:579–584
3. Vogl TJ, Gruber T, Balzer JO, Eichler K, Hammerstingl R, Zangos S (2009) Repeated transarterial chemoembolization in the treatment of liver metastases of colorectal cancer: prospective study. Radiology 250:281–289
4. Albert M, Kiefer MV, Sun W et al (2011) Chemoembolization of colorectal liver metastases with cisplatin, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol. Cancer 117:343–352
5. Akinwande O, Scoggins C, Martin RC (2016) Early experience with 70-150 mum Irinotecan drug-eluting beads (M1-DEBIRI) for the treatment of unresectable hepatic colorectal metastases. Anticancer Res 36:3413–3418
6. Loffroy R, Lin M, Yenokyan G et al (2013) Intraprocedural C-arm dual-phase cone-beam CT: can it be used to predict short-term response to TACE with drug-eluting beads in patients with hepatocellular carcinoma? Radiology 266:636–648
7. Akinwande O, Philips P, Scoggins CR et al (2016) Comparison of tumor response assessment methods in patients with metastatic colorectal cancer after locoregional therapy. J Surg Oncol 113:443–448
8. Zhuang ZG, Zhang XB, Han JF et al (2014) Hepatic blood volume imaging with the use of flat-detector CT perfusion in the angiography suite: comparison with results of conventional multislice CT perfusion. J Vasc Interv Radiol 25:739–746
9. Lencioni R, Aliberti C, de Baere T et al (2014) Transarterial treatment of colorectal cancer liver metastases with irinotecan-loaded drug-eluting beads: technical recommendations. J Vasc Interv Radiol 25:365–369
10. Zellerhoff M, Deuerling-Zheng Y, Strother CM et al (2009) Measurement of cerebral blood volume using angiographic C-arm systems. Proc. SPIE 7262, Medical Imaging 2009: Biomedical Applications in Molecular, Structural, and Functional Imaging, 72620H. https://doi.org/10.1117/12.812097
11. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
12. Shrout PE, Fleiss JL (1979) Intraclass correlations: uses in assessing rater reliability. Psychol Bull 86:420–428
13. Rao PP, Pascale F, Seck A et al (2012) Irinotecan loaded in eluting beads: preclinical assessment in a rabbit VX2 liver tumor model. Cardiovasc Intervent Radiol 35:1448–1459
14. Ganguly A, Fieselmann A, Marks M et al (2011) Cerebral CT perfusion using an interventional C-arm imaging system: cerebral blood flow measurements. AJNR Am J Neuroradiol 32:1525–1531
15. Struffert T, Deuerling-Zheng Y, Kloska S et al (2011) Cerebral blood volume imaging by flat detector computed tomography in comparison to conventional multislice perfusion CT. Eur Radiol 21:882–889
16. Struffert T, Deuerling-Zheng Y, Kloska S et al (2010) Flat detector CT in the evaluation of brain parenchyma, intracranial vasculature, and cerebral blood volume: a pilot study in patients with acute symptoms of cerebral ischemia. AJNR Am J Neuroradiol 31:1462–1469

17. Mueller K, Fahrig R, Manhart M et al (2016) Reproducibility of parenchymal blood volume measurements using an angiographic C-arm CT system. Acad Radiol 23:1441–1445
18. Syha R, Grözinger G, Grosse U et al (2016) Parenchymal blood volume assessed by C-arm-based computed tomography in immediate posttreatment evaluation of drug-eluting bead transarterial chemoembolization in hepatocellular carcinoma. Invest Radiol 51: 121–126
19. Vogl TJ, Schaefer P, Lehnert T et al (2016) Intraprocedural blood volume measurement using C-arm CT as a predictor for treatment response of malignant liver tumours undergoing repetitive transarterial chemoembolization (TACE). Eur Radiol 26:755–763
20. Kaufmann S, Horger T, Oelker A et al (2015) Characterization of hepatocellular carcinoma (HCC) lesions using a novel CT-based volume perfusion (VPCT) technique. Eur J Radiol 84:1029–1035
21. Kaufmann S, Horger T, Oelker A et al (2015) Volume perfusion computed tomography (VPCT)-based evaluation of response to TACE using two different sized drug eluting beads in patients with nonresectable hepatocellular carcinoma: impact on tumor and liver parenchymal vascularisation. Eur J Radiol 84:2548–2554
22. Pereira PL, Krüger K, Hohenstein E et al (2018) Intraprocedural 3D perfusion measurement during chemoembolisation with doxorubicin-eluting beads in liver metastases of malignant melanoma. Eur Radiol 28:1456–1464
23. Reiner CS, Morsbach F, Sah BR et al (2014) Early treatment response evaluation after yttrium-90 radioembolization of liver malignancy with CT perfusion. J Vasc Interv Radiol 25:747–759
24. Boas FE, Brody LA, Erinjeri JP et al (2016) Quantitative measurements of enhancement on preprocedure triphasic CT can predict response of colorectal liver metastases to radioembolization. AJR Am J Roentgenol 207:671–675
25. Ruers T, Punt CJ, van Coevorden F et al (2015) Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): long-term survival results of a randomized phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC). J Clin Oncol 33:3501–3501