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INTERVENTIONAL

Intraprocedural blood volume measurement using C-arm CT as a predictor for treatment response of malignant liver tumours undergoing repetitive transarterial chemoembolization (TACE)

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Abstract

Purpose To evaluate feasibility of measuring parenchymal blood volume (PBV) of malignant hepatic tumours using C-arm CT, test the changes in PBV following repeated transarterial chemoembolization (TACE) and correlate these changes with the change in tumour size in MRI.

Methods 111 patients with liver malignancy were included. Patients underwent MRI and TACE in a 4- to 6-week interval. During intervention C-arm CT was performed. Images were post-processed to generate PBV maps. Blood volume data in C-arm CT and change in size in MRI were evaluated. The correlation between PBV and size was tested using Spearman rank test.

Results Pre-interventional PBV maps showed a mean blood volume of 84.5 ml/1000 ml±62.0, follow-up PBV maps after multiple TACE demonstrated 61.1 ml/1000 ml±57.5. The change in PBV was statistically significant (p=0.02). Patients with initial tumour blood volume >100 ml/1000 ml dropped 7.1 % in size and 47.2 % in blood volume; 50–100 ml/1000 ml dropped 4.6 % in size and 25.7 % in blood volume; and <50 ml/1000 ml decreased 2.8 % in size and increased 82.2 % in blood volume.

Conclusion PBV measurement of malignant liver tumours using C-arm CT is feasible. Following TACE PBV decreased significantly. Patients with low initial PBV show low local response rates and further increase in blood volume, whereas high initial tumour PBV showed better response to TACE.

Key Points

- *Parenchymal blood volume assessment of malignant hepatic lesions using C-arm CT is feasible.*
- *The parenchymal blood volume is reduced significantly following transarterial chemoembolization.*
- *Parenchymal blood volume can monitor the response of tumours after transarterial chemoembolization.*
- *Although not significant, high initial parenchymal blood volume yields better response to TACE.*

Keywords Liver · Neoplastic processes · Therapeutic chemoembolization · Perfusion · Computed tomography

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Introduction

Cancer is the leading cause of death worldwide. The reported number of deaths because of liver cancer worldwide in 2008 was 695,000 patients [1] and hepatocellular carcinoma (HCC) is the third most common cause of cancer mortality with still rising incidence [2]. A curative resection can only be performed in 15–20 % [3]. Other treatment options include systemic chemotherapy, local ablative procedures or transarterial chemoembolization (TACE). TACE is a well-established procedure and can be used not only as a palliative treatment but also as a preparatory step for a curative treatment [4, 5].

Currently the response of cancer lesions to a treatment is mainly based on size measurement according to the RECIST criteria. This does not include any form of assessment of the change in tumour vascularity although this is one of the main targets of the chemoembolization procedures. Further examinations like perfusion-CT or perfusion-MRI would have to be performed in order to get this information. In addition, it has been shown that CT-derived dynamic parameters, i.e. blood flow (BF), blood volume (BV) and mean transit time (MTT), correlate with histological measurements of angiogenesis [6]. CT perfusion has been suggested as a method for early assessment of response after TACE in a rabbit model [7] and after anti-angiogenic treatment [8]. C-arm CT is a recently introduced facility in the angiography suite that facilitates intraprocedural 3D soft tissue images of the whole liver [9]. This makes it possible to infer parenchymal blood volume (PBV) of the liver during the intervention.

The current study was formulated to test the feasibility of measuring the PBV using C-arm CT and to assess the possible changes in PBV following TACE and whether these changes correlate with the patient response to TACE based on changes in tumour size.

Materials and methods

The study was approved by the institutional ethical committee. Informed consent was obtained from all patients. From October 2010 till December 2011, 111 patients (49 male, 62 female) with liver tumours, classified as non-resectable, underwent repetitive MRI and TACE in a 4- to 6-week interval [10–14] with 2–10 sessions per patient (mean 3.8, SD= 1.85). At the time of the initial chemoembolization, the patients' age was between 19 and 83 years (mean 61.5, SD= 12.2).

Table 1 Number and type of primary cancer groups evaluated in our study and their mean PBV values before and after treatment

Tumour	No. included in study
Liver metastasis of breast cancer	33
Liver metastasis of colorectal cancer	27
CCC	13
HCC	12
Liver metastasis of pancreatic cancer	9
Liver metastasis of gastric cancer	3
Liver metastasis of lung cancer	3
Liver metastasis of ovarian cancer	2
Liver metastasis of oesophageal cancer	2
Liver metastasis of leiomyosarcoma	2
Liver metastasis of melanoma	1
Liver metastasis of nasopharyngeal cancer	1
Liver metastasis of thymoma	1
Haemangiopericytoma	1
Neuroblastoma	1

Colonic cancer includes cancer of all parts of the colon. CCC includes Klatskin tumours and gallbladder cancer

The origin of the malignant hepatic lesions in our patient group is shown in Table 1. The decision for choosing chemoembolization as a treatment for the patients was made in an interdisciplinary tumour board.

Inclusion and exclusion criteria

The inclusion criteria were age above 18 years and non-resectable liver metastases showing no response, disease progression or toxicity to systemic chemotherapy. The presence of extrahepatic metastases was excluded by means of abdominal and chest computed tomographic (CT) imaging. Before each session of treatment, specific laboratory values were checked to ensure that the patient did not have any exclusion criteria or any contraindication to chemoembolization treatment.

Exclusion criteria were poor performance status (Karnofsky status, ≤70 %, ECOG grade (PS) ≥2), nutritional impairment, presence of marked ascites, high serum total bilirubin level [>3 mg/dL (51.3 μmol/L)], poor hepatic synthesis [serum albumin level <2.0 mg/dL (20 g/L)], renal failure [serum creatinine level >2 mg/dL (176.8 μmol/L)] and patients with Child–Pugh C classification; partial or complete thrombosis of the main portal vein was a further exclusion criterion for the procedure, as was cardiovascular or respiratory failure. The tumour load of the liver was restricted to not more than 70 % of the total liver volume.

To ensure adequate treatment compliance, the patients had to be in a good mental state and had to be able to provide their own consent. All patients signed an informed consent before TACE and MRI examination.

MRI protocol

The initial patient evaluation was performed by contrast-enhanced MRI and then followed by repetitive TACE and C-arm CT with a treatment interval of 4–6 weeks. Non-contrast-enhanced MRI before each TACE monitored response to chemoembolization treatment. Primary end points were a re-evaluation of the tumour as curative treatable or non-responder.

A 1.5-T system (Magnetom Avanto; Siemens, Erlangen, Germany) was used to acquire unenhanced MRI and in the absence of any contraindications contrast-enhanced MRI, with 0.1 mmol/kg body weight of gadobutrol (Gadovist; Bayer Healthcare AG, Leverkusen, Germany) or gadoteric acid (Dotarem; Guerbet, Sulzbach, Germany) was performed. The MRI protocol included T1-weighted, unenhanced and

contrast-enhanced, two-dimensional, fast low-angle shot gradient-echo sequences with transverse and sagittal section orientation [repetition time (ms)/echo time (ms) 135/6, flip angle 80°, field of view (FOV) 350 mm, matrix 134×256, section thickness 8 mm]. In addition, unenhanced T2-weighted turbo spin-echo sequences (3800/92, flip angle 150°, FOV 350 mm, matrix 155×256, section thickness 8 mm) and dynamic volume interpolated breath-hold examination sequences (4.5/1.8, flip angle 15°, FOV 350 mm, matrix 128×256, section thickness 8 mm) were used after administration of a contrast medium.

TACE protocol

All TACE procedures were performed by a single interventionist (with more than 20 years' experience in interventional radiology) to ensure consistency. The procedures were carried out using a Siemens Artis® Zeego system (Siemens AG Healthcare Sector, Forchheim, Germany).

After ensuring local anaesthesia a selective catheter was introduced through the right femoral artery using the Seldinger technique. The vascular anatomy of the abdominal aorta and the hepatic arteries was determined. The catheter was then advanced beyond the gastroduodenal artery. Depending on size, location and arterial supply of the lesion, the tip of the catheter was advanced further into the segmental or subsegmental arteries and chemoembolization agents were injected carefully. None of the patients underwent global TACE. Segmental or subsegmental chemoembolization was performed in all patients.

The chemotherapeutic suspension consisted of a patient-adapted dose of mitomycin, irinotecan, gemcitabin or cisplatin alone or in combination according to the tumour type. Vascular occlusion was performed after the injection of the chemotherapeutic suspension using a maximum dose of 10 ml iodized oil (Lipiodol®, Guerbet, Sulzbach, Germany) and 5 ml starch microspheres (EmboCept®, Pharmacept, Berlin, Germany) under fluoroscopic guidance until stasis was observed. After embolization, the devascularization of the tumour was confirmed via angiography.

C-arm CT

C-arm CT was performed before chemotherapeutic injection during the course of the first TACE session. The second C-arm CT was performed during the course of the second TACE in order to assess the initial response of the tumour to TACE. The C-arm CT after treatment was performed during the course of the last planned session of TACE to set the new baseline of PBV in case the patient returned for further interventions after initial stabilization. For patients who received only two sessions of TACE the second C-arm CT was considered the C-arm CT after treatment. The acquisition consisted of two

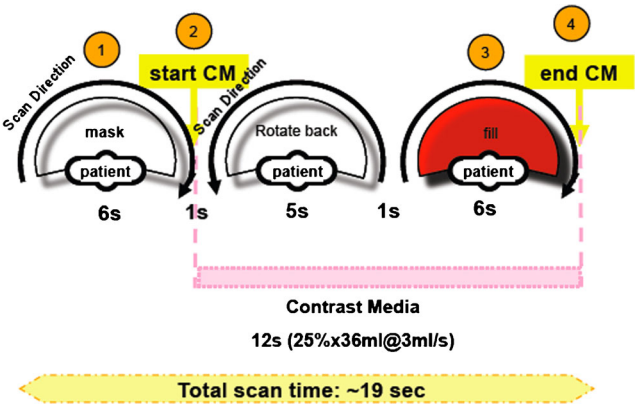

Fig. 1 Flow chart shows the acquisition protocol used to generate the blood volume images of the liver using an Artis Zeego System (Siemens). The patient is told to hold her/his breath shortly before the first rotation (mask run) starts (*1*). Right after finishing the mask run, manually triggered contrast injection is started (*2*) to ensure a constant contrast flow in the liver parenchyma. The C-arm rotates back and immediately starts the second rotation (fill run) (*3*). The overall scanning time of about 19 s was well tolerated by almost every patient

rotations: an initial rotation (mask run) followed by a second rotation after contrast medium injection (fill run) (Fig. 1). Both rotations were run during a single breath hold. Data acquisition per run was carried out using the following parameters: acquisition time 5 s, 90 kV, 616×480 matrix, projection on 30×40 cm flat panel size, 200° total angle, 0.8°/frame, 248 frames total, detector entrance dose 0.36 μGy/frame. Before the C-arm rotates back between the mask and fill runs, which takes another 5–6 s, the contrast was injected immediately after the mask run has been finished. The contrast was then distributed through the arteries and reached a homogeneous enhancement in the target lesions. We used 9 ml of contrast medium (Visipaque®, GE Healthcare, Munich, Germany) diluted to 25 % using normal saline that was injected into the hepatic artery at a rate of 3 ml/s using a power injector (Mark V ProVis, Medrad Inc®, Pittsburgh, Pennsylvania, USA).

Post-processing of C-arm PBV imaging

PBV post-processing was performed using a separate workstation (Syngo XWP, Siemens AG Healthcare Sector, Forchheim, Germany). We used a similar post-processing algorithm as previously described by Zellerhoff et al. [15].

Unlike conventional CT, C-arm CT has temporal resolution limitations where the C-arm cannot rotate rapidly enough to acquire several acquisitions over a period of time to deliver an enhancement curve as a function of time. Hence a different post-processing algorithm is required to process the data acquired by the C-arm CT. To overcome this problem a longer injection is used to achieve a steady state of contrast in the region of examination; this steady state will deliver

enhancement values for the tissue, artery and vein that are independent of time [15].

In summary, the mask and the fill run were reconstructed and subtracted. The mask and fill volumes were registered with a non-rigid motion-correction algorithm before subtraction. An algorithm to segment out air and bone is applied. The arterial input function value is calculated from an automated histogram analysis of the vessel tree. This arterial input function value is then applied as a scaling factor to obtain the quantitative PBV map. In a final step, a smoothing filter is applied to reduce pixel noise. The PBV map was then visualized with a colour map by the reader.

Data collection and statistical analysis

The MR images were interpreted by a radiologist with more than 10 years of experience in abdominal imaging. The PBV maps were evaluated by another two radiologists in consensus with more than 3 and 10 years of experience in abdominal imaging. The radiologists evaluating the MRI and PBV were double-blinded. A fourth radiologist (study coordinator) combined the results of the MRI and PBV maps and was not allowed to change the results of either. The radiologists evaluating the MRI and PBV were asked to mark the evaluated lesions on a schematic representation of the liver segments, to ensure accuracy of the final step, i.e. the combination of the MRI and PBV maps by the study coordinator.

The change in lesion size was assessed according to the RECIST system [16] based on the largest dimension of the target lesions as seen on MRI [17]. Blood volume data were acquired by forming regions of interest (ROI) around every detected lesion and tracking them over multiple sessions of therapy. MRI and blood volume images were fused and compared in corresponding axial planes. The patients were assessed in several groups depending on the origin of the liver lesions or values of the initial blood volume. The choice of the RECIST criteria instead of mRECIST for assessment of the tumour response in the current study was based on several points related to the study design. First RECIST represents the most widely used method of assessment of tumour response in general, especially among oncologists. Second, RECIST assessment represented a greater challenge to the method under investigation; although modified RECIST will assess the tumour enhancing areas, it is obvious that the blood volume will correlate with the enhancement, so the challenge was whether the assessed blood volume correlates with the size change or not. Finally the blood volume was assessed for the whole tumour and not for enhancing areas only, so for accurate correlation of the changes a standard widely accepted measurement (namely RECIST) was required to include the whole tumour and not only the enhancing areas of the tumour.

The clinical data were recorded as provided to us by the referring oncologists. The complications and adverse effects were documented from the obtained imaging studies and from post-interventional monitoring. Abdominal pain, fever, nausea and vomiting after TACE were considered as post-embolization syndrome.

The patients were distributed into different subgroups depending on their primary tumour (hepatocellular carcinoma, colorectal carcinoma, breast cancer, others) and their initial blood volume data (<50, 50–100, >100 ml/1000 ml). Then, statistical analyses were performed and interpreted by a statistician using BiAS for Windows software (EPSILON-Verlag, Darmstadt, Germany). The correlation between the initial blood volume and change of size in MRI was tested by calculating Spearman's rho (ρ). The same method was used to correlate initial blood volume with the difference in blood volume from the first to the last session of therapy. In addition, the regression of initial blood volume and change in blood volume was calculated using a simple regression as described by Pearson.

Results

C-arm CT was technically successful in all cases and PBV maps could be obtained from all examinations. In total, we evaluated 247 lesions. The pre-interventional PBV measurement of all liver lesions demonstrated a mean value of 84.5 ml/1000 ml±62. The follow-up after the first session of TACE showed a mean reduction of PBV values of 13.1 ml/1000 ml from 84.5 to 71.4 ml/1000 ml±59.6. The reduction in PBV after the first TACE session was statistically significant ($p<0.0001$). After repeated TACE the mean value for all lesions was 61.1 ml/1000 ml±57.5. The reduction in PBV after the repeated TACE sessions was statistically significant ($p=0.02$). Figures 2 and 3 show examples of the PBV measurement and their corresponding MRI examinations.

Statistical analysis as described by Spearman and Kendell showed no significant correlation between PBV values before TACE and change of size measured in MRI (rho=0.05; $p=0.55$). After TACE, a correlation between PBV values and size changes in MRI showed similar results (rho=0.06; $p=0.51$). Changing of PBV values showed no statistically significant correlation with size changes in MRI (rho=0.05; $p=0.61$).

Follow-up MRI classified 14 patients as partial response (PR), 88 as stable disease and nine as progressive disease (PD), according to the RECIST criteria. Seven of the patients with PD had an initial blood volume of <50 ml/1000 ml (Table 2).

On subgroup analysis the HCC tumour group showed mean initial PBV values of 98.5 ml/1000 ml±91.9, colorectal metastases showed 64.0 ml/1000 ml±39.9 and breast cancer metastases had a mean value of 108.5 ml/1000 ml±72.9. The

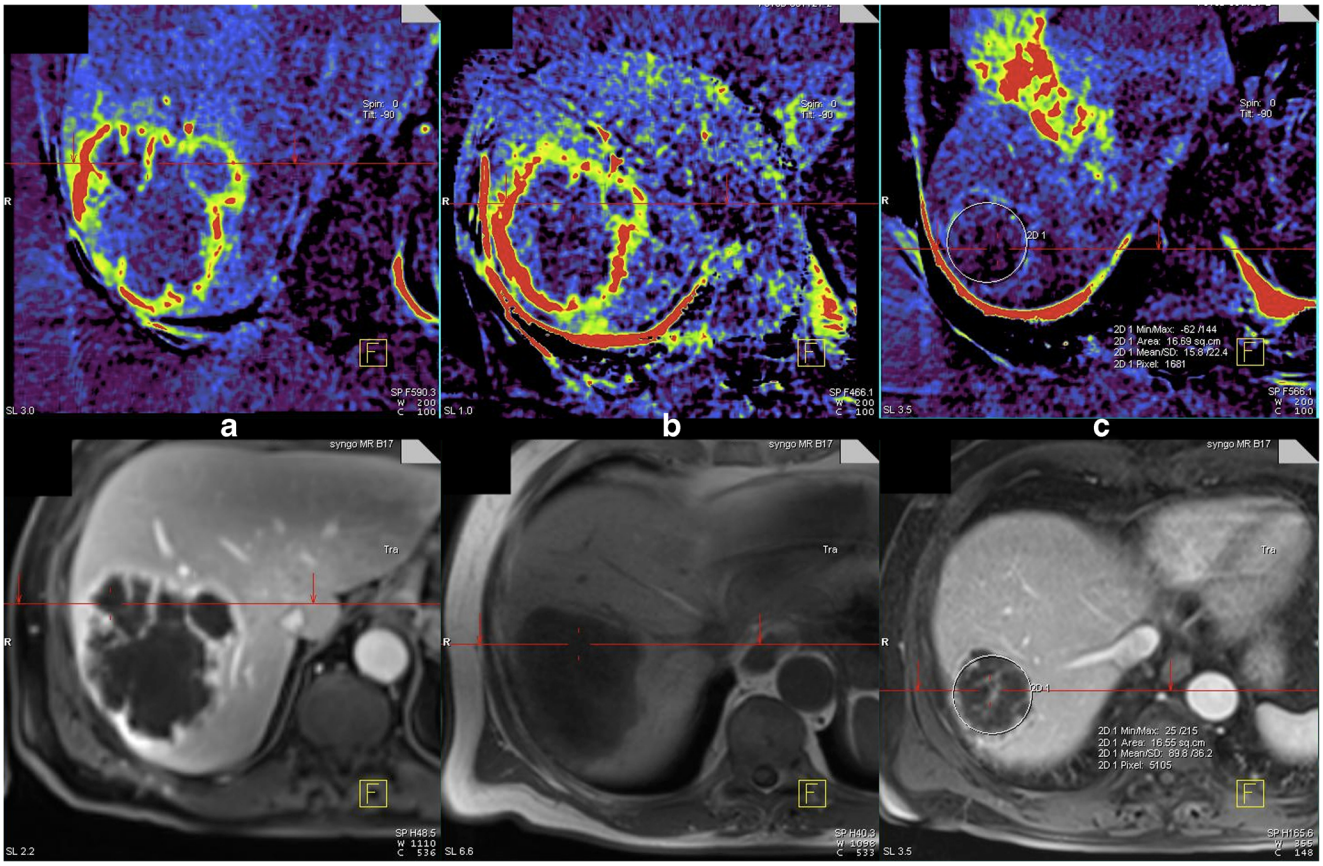

Fig. 2 A 73-year-old male patient with colorectal cancer liver metastasis showing a size reduction of 40.7 % (partial response after RECIST) and a decrease in blood volume of 59.7 %. The generated PBV images are shown in the *upper row* using the standard coloured (W=200, C=100) window with the *lower row* showing contrast-enhanced (*left* and *right*) and native T1-weighted (*middle*) MRIs of the liver. **a** Initial PBV and MRI images, **b** generated during the course of the second TACE treatment, **c** the lesions after 6 TACE sessions (last session)

blood volume of the HCC group dropped by 11.5 ml/1000 ml ±122.3 (= −11.7 %), that of colorectal metastasis decreased by 23.3 ml/1000 ml±47.9 (= −36.4 %) and that of metastasis of breast cancer was reduced by 33.3 ml/1000 ml±68.8 (= −30.7 %) (Table 3).

The difference in change of blood volume after therapy between the different tumour groups was not statistically significant (p>0.05).

Classifying the patients by initial blood volume resulted in three groups: group A with an initial blood volume >100 ml/1000 ml (n=37), group B with an initial blood volume 50–100 ml/1000 ml (n=37) and group C with an initial blood volume of <50 ml/1000 ml (n=37).

Group A dropped 7.1 % in size and 47.2 % in blood volume; group B dropped 4.6 % in size and 25.7 % in blood volume; and group C decreased 2.8 % in size and increased 82.2 % in blood volume (Table 2). A correlation analysis as described by Spearman and Kendall demonstrated a significant correlation between initial blood volume and the change in blood volume between the initial and the last PBV measurement (rho=0.61; p<0.0001). Subgroup analysis showed these findings to be consistent except for the group with HCC (due to low patient number) and patients with initial PBV values of 50–100 ml/1000 ml (Table 4).

Discussion

The best curative therapy of malignant liver tumours is partial hepatectomy. But with only 20 % treatable patients it has many limitations [3]. Unfortunately the mean survival of untreated patients with hepatic metastases of colorectal cancer for example is only 4.5–10 months [18, 19].

New and less invasive therapy options therefore represent a reasonable solution to be able to treat more patients. TACE is one of these options. To monitor and ensure the response of lesions treated with TACE, an objective and reproducible standard has to be established. Measuring the diameter of all lesions in MRI or CT and monitoring their progress (after RECIST criteria) is today's method of choice. However this does not cover dynamic parameters of tumor tissue, which are quite variable in different types of tumours.

Currently CT is routinely used to display vessel anatomy in CT-angiography (CTA) [20]. But CTA is still only the static

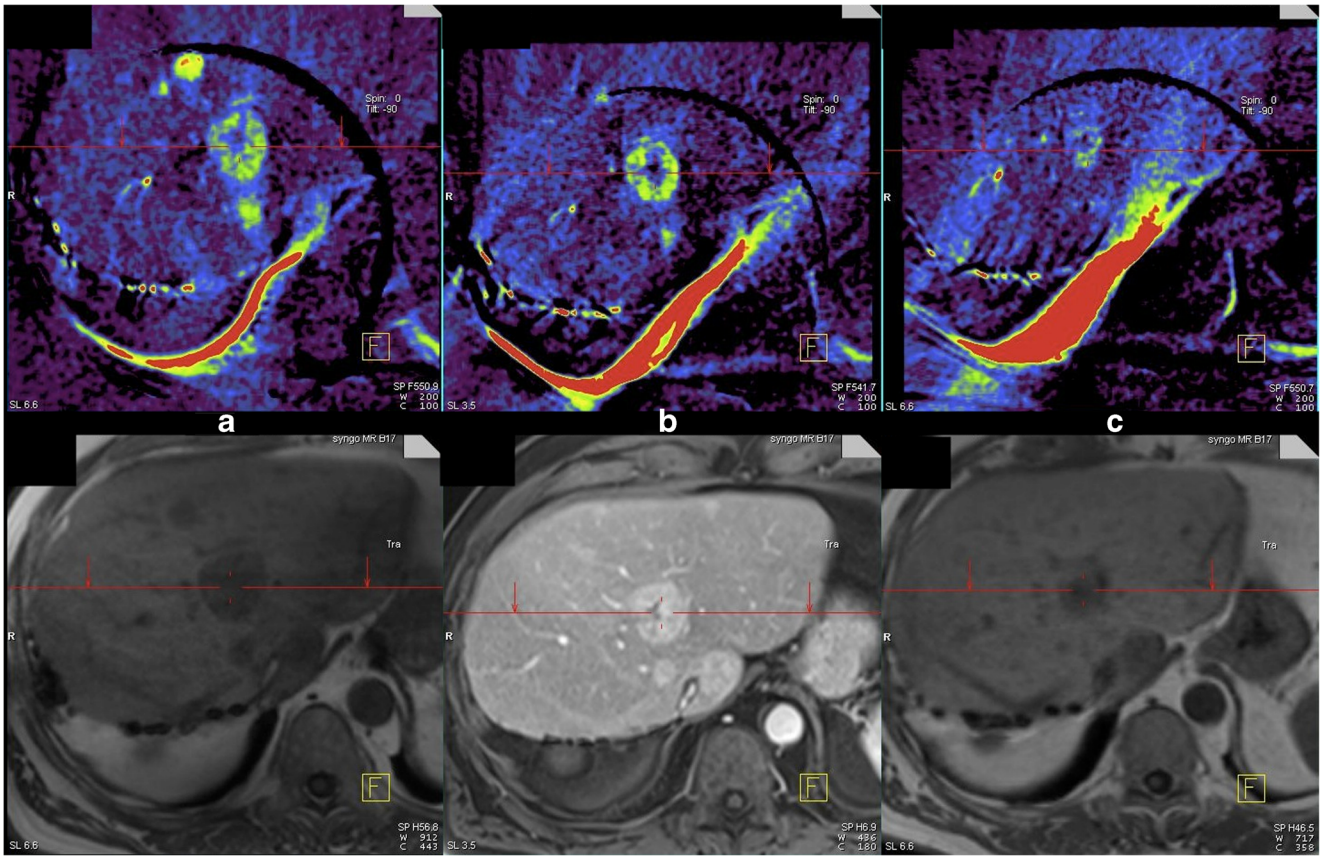

Fig. 3 A 71-year-old male patient with hepatocellular carcinoma showing a size reduction of 28.5 % in MRI (partial response after RECIST) and a decrease in blood volume of 26 %. The *three upper images* show the generated PBV images in the standard coloured (*W*=200, *C*=100) window, the *three lower images* show native (*left* and *right*) and contrast-enhanced MRIs of the liver. **a** Initial status, **b** during the course of the second TACE treatment and **c** after the third TACE session (last session)

readout of a dynamic process. Today functional imaging is becoming increasingly important in clinical daily practice. With current tomographs it is also possible to measure dynamic parameters like BF, BV or mean transit time MTT to assess tumour vascularity and angiogenesis as well [21]. There are even studies with promising results in the assessment of cerebral infarction with CT-derived 3D PBV maps [22]. Still the necessary CT has to be done before or after an interventional procedure. A C-arm CT has the possibility to provide functional, soft-tissue and vascular information in a single intra-procedural acquisition. This allows the monitoring of tumour sizes, vascularisation and blood volume in a minimized amount of extra time and resources for the patients and hospitals.

In a conventional CT perfusion scan a bolus of contrast medium is intravenously injected followed by a number of scans of the area of interest using a high temporal sampling rate, in this case the time–attenuation curve is used to calculate the different perfusion parameters. In this conventional method two issues are to be considered: first, the radiation exposure since the same volume will have to be scanned several times; second, the volume of the scan where under certain circumstances a smaller scan volume might be selected in order to allow the rapid sequential acquisition. Currently such a problem is much less encountered owing to the newly available

Table 2 Change in blood volume and size during treatment sorted by initial blood volume values

Mean BV (ml/1000 ml)	Diff BV (%)	Diff size in MRI (%)	PR	SD	PD	*n*
>100	−47.2	−7.1	6	29	2	37
50–100	−25.7	−4.6	6	31	0	37
<50	+82.2	−2.8	2	28	7	37

PR partial regression, *SD* stable disease, *PD* progressive disease (after RECIST)

Table 3 Correlations between initial blood volume and change in blood volume after therapy for different patient collectives and their level of significance

Lesion type	Initial mean PBV	Follow-up mean PBV	Diff. (%)	*n*
Metastasis of breast carcinoma	108.5	75.2	−30.7	33
Metastasis of colorectal carcinoma	64.0	40.7	−36.4	27
CCC	68.8	44.5	−35.4	13
HCC	98.5	86.9	−11.7	12
Metastasis of pancreatic carcinoma	63.3	37.5	−40.8	9
Metastasis of gastric carcinoma	78.73	67.6	−14.14	3
Other metastasis	84.7	74.1	−12.5	14

Colonic cancer includes cancer of all parts of the colon. CCC includes Klatskin tumours and gallbladder cancer

scanners covering up to 16 cm of scan per gantry rotation. The third problem is the arrival of contrast medium bolus which is affected by several factors including the venous line used and the cardiac function of the patient. For C-arm CT perfusion, the speed of C-arm rotation will limit the temporal resolution; hence only two scans are performed and the post-processing of the data is quite different from the conventional method. The issue of bolus injection is obviously almost abolished here since the contrast medium is directly injected into the feeding artery of the region of interest; hence a more homogenous bolus is achieved with little effect of the systemic circulation and cardiac function. In spite of that it is important to remember that the issue of radiation exposure should not be ignored and should be kept in consideration: in particular, the information available regarding the radiation exposure during C-arm CT compared to conventional CT is still missing and needs to be verified through research studies.

Although not significant, we could find a correlation between initial blood volume and response to TACE measured as size reduction in MRI. We observed a wide variation of the measured PBV values which was most obvious in the initial analyses; we attribute this variation to the highly inhomogeneous patient collective.

The patients with higher initial blood volume showed the most pronounced decrease in PBV and lowest incidence of progressive disease after TACE. This could support our initial assumption that higher blood volume levels accompany larger cytotoxic effects of the chemotherapy and therefore end up in a better response to treatment. Furthermore patients with lesions having an initial PBV of less than 50 ml/1000 ml even showed an increase in PBV following treatment, which is also reflected in the very small reduction in size observed in those patients. This supports the fact that hypovascular malignant hepatic lesions will not show a favourable response to TACE.

Table 4 All included lesion types: initial BV correlated with change of BV

	Rho	*p*	*n*
All	−0.61	<0.0001	111
Breast cancer	−0.61	<0.001	33
Colorectal cancer	−0.59	<0.01	27
HCC	−0.68	<0.1	12
>100 ml/1000 ml	−0.32	0.05	37
50–100 ml/1000 ml	−0.22	0.23	32
<50 ml/1000 ml	−0.54	<0.0001	37

Bley et al. [23] showed that C-arm CT works well in detecting cerebral blood volume and potentially salvageable brain tissue after ischaemic stroke [24]. By adapting the acquisition protocols to liver imaging we could achieve equal image quality. A comparison with CT perfusion would make sense, but Ng et al. [25] showed that CT perfusion measurements of liver tumours have wide variances in absolute values and reproducibility. This is what we also recognized in our data. On the other hand, regarding advanced HCC, Sahani et al. showed CT perfusion to be a feasible and reproducible technique for evaluating tumour vascularity and angiogenesis [26]. We therefore expect CT perfusion to gain more and more influence and C-arm CT to be the next step in monitoring success of TACE.

Our study has some shortcomings. Doing a pilot study we included several different types of primary liver tumours and liver metastases; however, despite the heterogeneity of the patients, we did not find a statistically significant difference between the different groups of tumours regarding the PBV parameters tested. In future evaluations larger patient collectives with the same type of malignant lesions should be performed to gain more statistically reliable results. Furthermore the heterogeneous origin of the treated tumours required several chemotherapeutic agents to be used in the current study, which might also have an influence on the results. Here it is important to emphasize that some tumour entities were treated within an off-label use concept for palliative indication after failure of the different systemic regimens. Thus further studies addressing the same tumour type and using the same

chemotherapeutic agents are required. The third limitation is that the last C-arm CT used to represent the new baseline PBV of the patient after the last TACE session was measured before the last embolization (since C-arm CT was always performed before the injection of any medications or embolizing material). Therefore the last PBV does not represent the most accurate new baseline. However, a C-arm CT immediately after embolization would not have been accurate either because of the possible redistribution process of the embolizing material after injection and because of the tumour neovascularization, which might also play a role. Thus we preferred the first option.

To conclude, parenchymal blood volume assessment using C-arm CT is a feasible technique that can be performed during the course of transarterial chemoembolization. Following repeated TACE the PBV drops significantly and thus this parameter can be introduced for monitoring response to treatment following TACE. Although not significant patients with initially high levels of PBV showed better response than those with low initial PBV.

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