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Parenchymal Liver Blood Volume and Dynamic Volume Perfusion CT Measurements of Hepatocellular Carcinoma in Patients Undergoing Transarterial Chemoembolization

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Abstract. *Aim: Prospective comparison of cone beam C-Arm CT based parenchymal liver blood volume (PLBV) and dynamic volume perfusion CT (dVPCT) measurements in patients with hepatocellular carcinoma (HCC) undergoing transarterial chemoembolisation (TACE) with drug-eluting beads (DEB). Patients and Methods: In 16 patients, changes of PLBV and dVPCT measurements [arterial liver parenchyma (ALP); temporal maximum intensity projection (MIP); hepatic perfusion index (HPI); portal venous parenchyma] were correlated to one another and to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Results: After TACE, the following parameters showed a statistically significant change ($p<0.05$) in mean value: PLBV: −4.85 ml/100 ml, ALP: −4.14 ml/100 ml/min, MIP: −0.23 Houndsfield units, HPI: −5.39%, and mRECIST: −20.53 mm. Pre-to-post TACE differences in PLBV showed only weak to very weak correlation to dVPCT parameters ($r^2<0.24$). Conclusion: Although PLBV and dVPCT parameters showed only a weak to very weak correlation, both methods validly assessed changes in arterial tumor vascularity after DEB TACE.*

Assessing response of hepatic malignancies to various therapies is often performed according to length measurements such as the Response Evaluation Criteria in Solid Tumors (RECIST) or modified RECIST (mRECIST) (1, 2). Methods, that can determine tumor response to certain therapy at an early stage would be more favorable. Different methods were used in studies with the arm of answering this question (3-5). With latest developments in image acquisition and intervention guidance, such as cone beam C-Arm CT (CBCT)-based measurements of parenchymal liver blood volume (PLBV), and dynamic volume perfusion CT (dVPCT) measurements with multidetector CT scanner (MDCT), new opportunities have opened up for early assessment of therapy response (4). Recent reports about peri-interventional assessment of PLBV measurements suggest a possible correlation of changes in PLBV after transarterial chemoembolisation (TACE) with tumor response (6). Since dVPCT and PLBV measurements are based on different image acquisition methods it is currently undetermined whether both methods can be correlated to one another and therefore replace one another, or can be used as a surrogate parameter for early response. The aim of this study was therefore to compare PLBV, dVPCT and diameter-based measurements to find a possible correlation with early therapy response in hepatocellular carcinoma (HCC) to TACE.

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Key Words: PLBV, DEB TACE, HCC, cone beam CT.

Patients and Methods

The Institutional Review Board approved the study (2014-401M-MA-§ 23b MPG). This prospective study was conducted as part of a research initiative comparing flat-panel CBCT (Artis zeego; Siemens Healthcare GmbH, Forchheim, Germany) and a dual-source MDCT (SOMATOM Force, Siemens Healthcare GmbH, Forchheim, Germany).

Study design. Inclusion criteria for the study was the decision for TACE by the local Interdisciplinary Tumor Board defining the patient not eligible for liver transplantation, surgery, or local ablative treatments according to European recommendations (7). Exclusion criteria were any contraindication for TACE.

Contraindication for drug-eluting beads (DEB) TACE were a plasma creatinine level above 2.0 mg/ml, an international normalized ratio (INR) above 2.0, a bilirubin level above 2.0 mg/dl, and a more than five-fold increase in transaminase levels.

Initially 25 patients gave their written informed consent to study inclusion. Nine patients had to be excluded from data analysis because no pre/post TACE dVPCT was obtained. Overall 16 patients and 17 lesions were included in the data analysis.

Treatment protocol. TACE was performed using a transfemoral approach. The diagnostic catheter was placed into the common hepatic artery to perform an angiogram of the hepatic vessel anatomy with different angulations to identify the tumor-feeding arteries. A coaxial microcatheter system (Progreat; Terumo, Eschborn, Germany) was advanced superselectively into the tumor-feeding artery for embolization. Chemoembolization was performed with a maximum dose of 75 mg doxorubicin DEB of 30-60 μm in size (Hepasphere™ microsphere; Merit Medical, South Jordan, UT, USA) until observation of stasis. Control hepatic angiography was repeated after embolization to ensure patency of the main hepatic arteries.

Measurement of PLBV. Before and after DEB TACE, a contrast-enhanced CBCT was performed: The process started with a non-enhanced mask run (5 seconds) with breath-hold. After the rotation of the C-arm back to the starting position (5 seconds), contrast medium injection started *via* the coaxial microcatheter using a flow rate of 3 ml/s and a volume of 36 ml (12 ml contrast medium diluted with 24 ml saline). Contrast-enhanced fill run (5 s) was performed in breath-hold 8 s after the start of contrast medium injection. The overall PLBV acquisition took 23 s. The microcatheter was placed either in the right or left hepatic artery depending on blood flow and collateral arteries to ensure proper flow of contrast medium into the tumor-feeding arteries.

The targeted liver lesions were evaluated on a commercial post-processing workstation (syngo XWP; Siemens Healthcare GmbH). For PLBV measurement, the ratio of the hypervascularized HCC lesion ($PLBV_{Tumor}$) and the normal liver parenchyma ($PLBV_{Liver}$) was calculated by placing three regions of interest (ROI) within the HCC lesion being treated and one ROI was placed within the normal liver parenchyma in the same slice. This was performed on three different slices resulting in nine $PBLV_{Tumor}$ ROI and three $PLBV_{Liver}$ ROI. The same procedure with the same microcatheter position was performed after DEB TACE.

Dynamic volume perfusion CT measurement. Similarly to Wang *et al*., dVPCT was performed with the MDCT system (8). Scan parameters were as follows: 70 kVp tube voltage (80 kVp if body mass index was above >33 kg/m^2), 190 mAs tube current time-product at 70 kVp, or 220 mAs at 80 kVp respectively, 48×1.2 collimation, 4-dimensional spiral mode with variable pitch with a z-axis coverage of 22.4 cm. The total image acquisition time was 71.2 s obtained by an 18 spiral acquisition and an inter-scan delay of 2×3 s, 10×1.5 s, 3×6 s, 2×15, 1×18. The examination was started 10 s after contrast injection: 50 ml iodinated contrast medium (Iomeprol 400; Bracco Imaging S.p.A., Milan, Italy) using venous access best placed in a cubital vein. Flow-rate was 5 ml/s using a power injector (Stellant® D CT Injection System; MEDRAD, Inc., Warrendale, USA) followed by a 50 ml saline chaser with the same flow rate. The patients were asked to hold their breath as long as possible and then to continue with a shallow breathing through the nose.

Table I. *Baseline characteristics. Patient age, time from dynamic volume perfusion computed tomographic (dVPCT) imaging to transarterial chemoembolization (TACE), time from TACE to CT imaging, and the dose of doxorubicin used in therapy are given.*

Baseline characteristic	Median (range)
Patient age (years)	72 (59-78)
Time from dVPCT to TACE (d)	1 (0-6)
Time from TACE to dVPCT (d)	1 (0-8)
Dose of doxorubicin (mg)	17 (8-75)

The dVPCT images were analyzed after reconstruction of the MDCT raw data using a commercial post-processing, multi-modality workstation (syngo.via; Siemens Healthcare GmbH). Three ROI were placed in a single slice within the treated HCC lesion and one ROI was placed in the healthy liver parenchyma in correlation to the PLBV analysis. This was performed within three different slices. The calculated values of arterial liver parchenyma (ALP; ml/100 ml/min), portal venous parenchyma (PVP; ml/100 ml/min), temporal maximum intensity projection [MIP; Hounsfield units (HU)], and hepatic perfusion index (HPI; %) were used for statistical analysis.

Additionally, the arterial phase images were used for dimensional lesion measurement before and after DEB TACE according to mRECIST, for which only the hypervascular part of the HCC lesion was measured (1). Objective response (OR) was defined as stable disease (SD), partial response (PR), and complete response (CR) in contrast to progressive disease (PD).

Statistical analysis. Statistical analysis was performed using JMP 11.0 (SAS Institute, Cary, NC, USA). Data were tested for normal distribution using the Shapiro–Wilk test. Pre- and post-therapy PLBV, ALP, PVP, HPI and dimensional measurements were compared using the Wilcoxon signed-rank test. Additionally, the differences between pre- and post-therapy PLBV, ALP, PVP, HPI and dimensional measurements were analyzed using multivariate analysis: with r^2:0.00 to 0.19 being considered very weak correlation, r^2:0.20 to 0.39 weak, r^2:0.40 to 0.59 as moderate, r^2:0.60 to 0.79 as strong, and r^2:0.80 to 1.0 as very strong correlation. Two-tailed *p*-values of less than 0.05 were considered statistically significant.

Results

HCC was proven histologically in 14 patients (88%) and in 2 patients by cross-sectional imaging (13%). According to the Barcelona Clinic Liver Cancer (BCLC) tumor staging, 13 patients had BCLC stage B (81%), and 3 patients had BCLC stage D (19%). HCC was caused by hepatitis infection in 6 patients (38%), alcohol abuse in 3 (19%), nonalcoholic fatty liver disease in 2 (13%), primary biliary cirrhosis in 1 (6%), and was autoimmune in 1 (6%) and cryptogenic in 3 (19%). Table I shows baseline characteristics for the patients, imaging and TACE.

PLBV, ALP, MIP, HPI and the diameter measurements decreased statistically significant after DEB TACE ($p<0.05$;

Table II. *Changes of the specific evaluated values of the cone beam C-Arm computed tomographic scan (CBCT) and of the dynamic volume perfusion computed tomographic scan (dVPCT).*

Variable		Mean value before (range)	Mean value after (range)	Mean change (range)	*p*-Value
CBCT	PLBV (ml/100 ml)	7.85 (1.58-21.3)	3.01 (0.54-10.54)	−4.85 (−0.38-20.13)	<0.0001
dVPCT	ALP (ml/100 ml/min)	5.27 (0.44-29.75)	1.13 (0.28-4.98)	−4.14 (0.0-28.76)	<0.0001
	PVP (ml/100 ml/min)	0.24 (0.3-1.99)	0.57 (0.04-2.32)	0.23 (−2.1-1.57)	0.3225
	MIP (HU)	1.11 (0.78-1.56)	0.88 (0.66-1.16)	−0.23 (0.0-0.56)	<0.0001
	HPI (%)	7.96 (1-55.28)	2.56 (0.54-8.03)	−5.39 (−2.73-54.34)	0.0033
	mRECIST (mm)	41.35 (20-94)	20.82 (0-65)	−20.53 (8-70)	<0.0001

PLBV: Parenchymal liver blood volume ratio; ALP: arterial liver parchenyma; PVP: portal venous parenchyma; MIP: temporal maximum intensity projection; HPI: hepatic perfusion index; mRECIST: modified Response Evaluation Criteria in Solid Tumors.

Table II). Only PVP values did not change statistically significantly after therapy (Table II): PVP increased by a mean of 0.23±0.21 ml/100 ml/min (p=0.3225). According to mRECIST evaluation of the contrast-enhanced CT scan before and after DEB TACE, all target lesions decreased in vascularity: mean decrease of vascularity was 49% (range: −18 to −100%; 100% OR). Figure 1 shows changes of a target lesion in angiography after TACE and Figure 2 shows changes in PLBV after TACE of the same patient.

Regarding the multivariate analysis of the pre-to-post differences of PLBV with the dVPCT parameters and mRECIST, only a weak to very weak correlation was found (Table III). The changes in HPI were found to correlate with the intra-individual differences of ALP (r^2=0.95). Additionally, the differences of MIP and mRECIST diameters showed a moderate correlation (r^2=0.45). For the other variables, only a weak to very weak correlation was found ($r^2 \leq 0.24$).

Table III. *Correlation of cone beam C-Arm computed tomographic scan-derived parenchymal liver blood volume (PLBV) and computed tomography perfusion-derived parameters.*

Parameter	Difference in PLBV (r^2)
Difference in ALP	0.1234
Difference in PVP	0.0606
Difference in MIP	0.2021
Difference in HPI	0.2388
Difference in mRECIST	0.0665

ALP: Arterial liver parchenyma; PVP: portal venous parenchyma; MIP: temporal maximum intensity projection; HPI: hepatic perfusion index; mRECIST: modified Response Evaluation Criteria in Solid Tumors.

Discussion

There have been several studies, which investigated which factors influence a non-response to TACE (9, 10). Ranieri *et al*. investigated changes of vascular endothelial growth factor (VEGF) and tryptase after DEB TACE in patients suffering from HCC. They found a statistically significant increase of approximately 124 pg/ml of VEGF (p<0.01) and a statistically significant decrease of approximately 4.11 μg/l of tryptase (p<0.01) following TACE and concluded that these laboratory values might be valid biomarkers indicating response to DEB TACE (9). Zhou *et al*. in a study with a rat model of HCC found that a combination of an anti-angiogenic saponin (Rg3) with TACE led to better overall survival and down-regulation of VEGF (5). In addition, Sciarra *et al*. in a study of patients with HCC reported that 44% of the study population was TACE resistant, which correlated with a diffuse staining of CD34 and negative staining of VEGF (p<0.05). With a weighted scoring system, they were able to predict TACE resistance with an accuracy of 81%, a sensitivity of 89% and a specificity of 59%. They concluded that this scoring system could have a potential value in prediction of TACE resistance (10). In addition to laboratory results, which seem to be able to predict therapy response to TACE, periinterventional imaging would also be preferable for early prediction of therapy failure. Peynircioğlu *et al*. performed CBCT and MDCT blood volume measurements in 14 hepatic tumor lesions (primary and secondary liver malignancies) in 10 patients undergoing TACE or radioembolization (11). The comparison of measurements by CBCT with those by MDCT showed a good correlation (r=0.97). They concluded that measurements with CBCT and MDCT were able to monitor changes of liver perfusion during therapy. Another study by Syha *et al*. also compared changes of parenchymal blood volume (PBV) with blood volume and blood flow measured by dVPCT after DEB TACE in 25 patients suffering from HCC (4). The overall correlation of PBV with blood volume

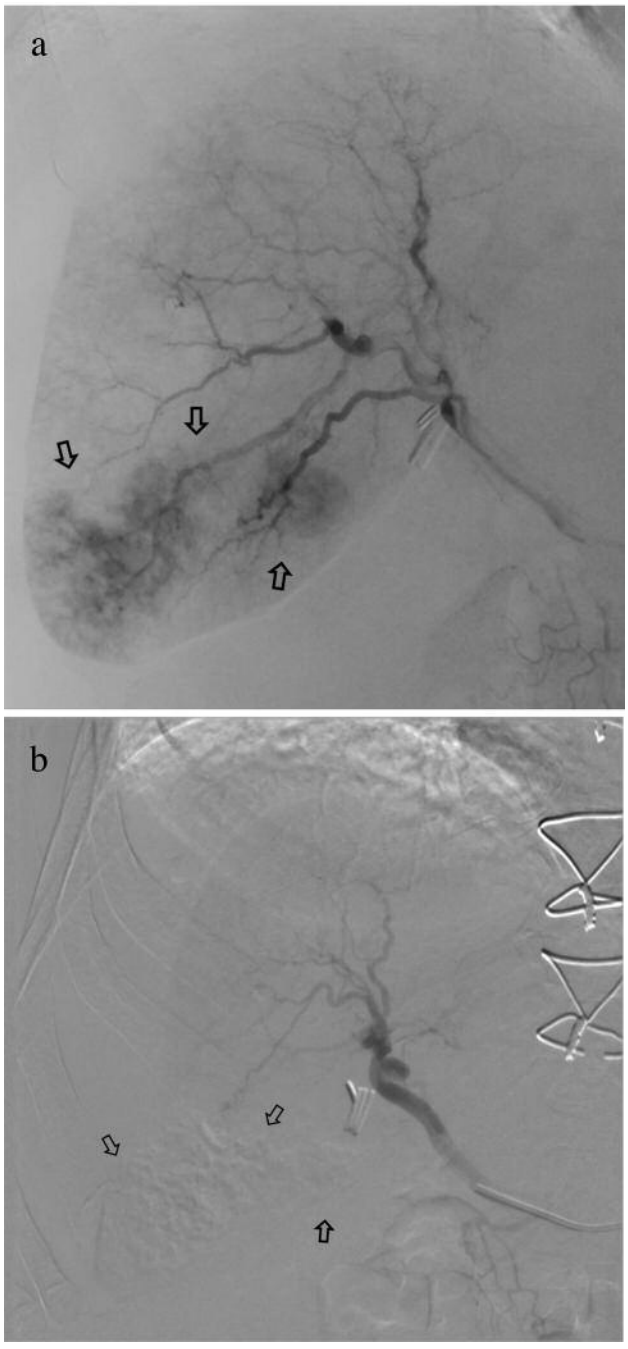

Figure 1. *Images showing angiography of the right hepatic artery. a: Hypervascularized target lesion (arrows) before therapy. b: Devascularized target lesion (arrows) after therapy.*

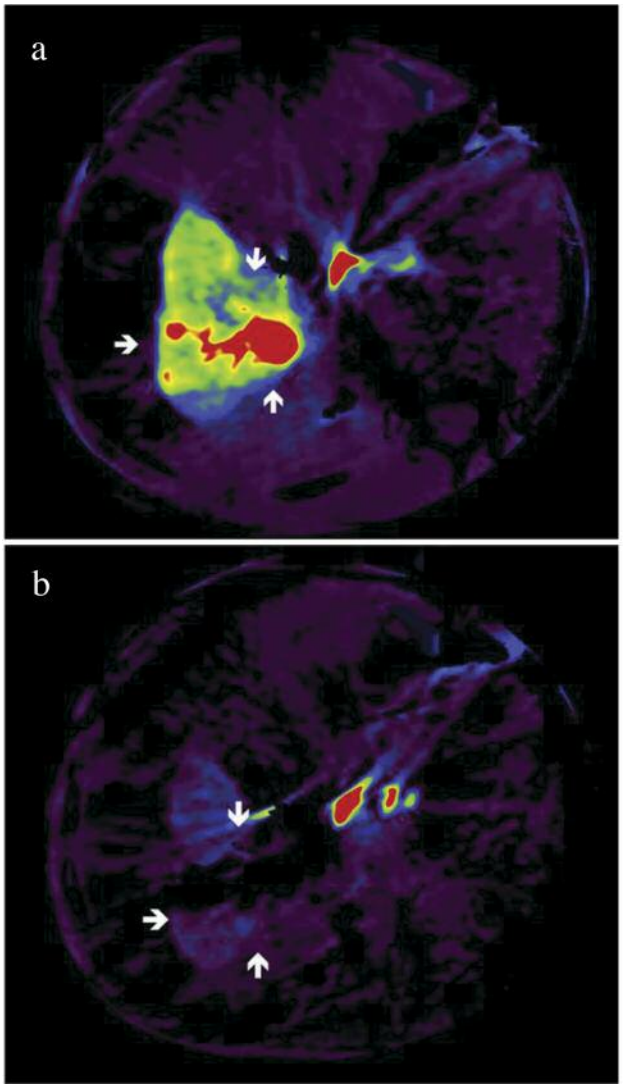

Figure 2. *Parenchymal liver blood volume imaging of the hypervascularized target lesion (arrows) before selective drug-eluting beads transarterial chemoambolisation (DEB TACE) (a) and devascularized target lesion (arrows) after DEB TACE (b). Colors encode areas of blood volume, from blue indicating low volume to red indicating a high volume.*

was weak (rho=0.24) to moderate (rho=0.45) depending on the different estimation models used. Additionally, they compared the perfusion parameter ratios of non-affected and tumor-affected liver parenchyma of the patient group with CR and PR to those with SD and PD. For PBV, blood flow, blood volume, ALP and HPI, the values increased in the group with OR compared to the group with SD or PD. They concluded that ratios of the perfusion parameters should be favorable for assessment of therapy response. Another study also found a reduced mid-term tumor response associated with residual increased PBV values (6).

Since all parameters measuring arterial tumor vascularity (PLBV, ALP, MIP, HPI, and mRECIST) decreased

statistically significantly after DEB TACE in the present study similarly to the well established mRECIST criteria, which also define therapy response by changes of arterial tumor vascularity, they seem to be able to assess therapy response. This is also in accordance with the results of Syha *et al*., which promote the ratios of the perfusion parameters as being able to assess therapy response. The lack of significant changes of PVP after DEB TACE indicates that there was not any significant change in portal venous blood flow as a reaction to tumor artery occlusion and this parameter does not seem to be useful for therapy assessment in this study setting. The lack of correlation of PLBV values with dVPCT and mRECIST values is in accordance with the results of Syha *et al*. and suggests that the measured parameters underlie independent changes. These results are contrary to those of Peynircioğlu *et al*. (11) and Zhuang *et al*. (12), who found a correlation of PBV measurements with blood volume MDCT measurements in hepatic malignancies. The differences might be explained by heterogeneities in the target lesions of the mentioned studies, since not only HCC lesions (primary vs. primary and secondary liver tumors) but also larger lesions were included in data analysis.

One limitation of our study is the study population, which was limited to 16 patients with an evaluation of 17 lesions. This is explained by poor patient compliance in undergoing the examinations (*e.g*. attending for dVPCT). Additionally, a correlation to overall survival would be preferable. Since patients suffering from HCC often undergo several TACE sessions, or different therapies might be performed in follow-up (*e.g*. local ablation techniques), definite correlation of imaging measurements with survival outcome is difficult. Further investigations with a larger study population are needed to demonstrate the value of PLBV and dVPCT in this context.

Although CBCT and dVPCT parameters showed only a weak to very weak correlation to each other, both methods validly assessed changes in arterial tumor vascularity after DEB TACE in HCC lesions and therefore might be used as surrogate parameters for tumor response. PLBV and dVPCT calculations immediately after TACE intervention could be considered for patient-tailored adaptation of time intervals for follow-up examinations.

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