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FULL PAPER

Feasibility of assessing pulmonary blood volume using C-arm CT during transpulmonary chemoperfusion and chemoembolization in primary and secondary lung tumours

¹THOMAS J VOGL, MD, ^{1,2}NOUR-ELDIN A NOUR-ELDIN, MSc, MD, ^{1,3}NAGY N N NAGUIB, MSc, MD,
¹THOMAS LEHNERT, MD, ⁴HANNS ACKERMANN, MD, ¹RENATE HAMMERSTINGL, MD and ¹MARCUS HEZEL

¹Institute for Diagnostic and Interventional Radiology, Johann Wolfgang Goethe University Frankfurt, Frankfurt, Germany

²Department of Diagnostic and Interventional Radiology, Faculty of Medicine, Cairo University, Egypt

³Department of Diagnostic and Interventional Radiology, Faculty of Medicine, Alexandria University, Egypt

⁴Department of Biomedical Statistics, Johann Wolfgang Goethe University Frankfurt, Frankfurt, Germany

Address correspondence to: Prof. Dr med. Thomas Josef Vogl
E-mail: t.vogl@em.uni-frankfurt.de

Thomas J Vogl and Nour-Eldin A Nour-Eldin contributed equally to this work.

Objective: Assessment of parenchymal blood volume (PBV) of primary and secondary pulmonary malignancies by using a C-arm CT, regarding its role in detecting early functional response to transpulmonary chemoembolization (TPCE) and clinical practicability.

Methods: 21 patients with a mean age of 56.77 years, who were assigned to TPCE during their palliative treatment, were included. PBV and the diameter of tumours were analyzed. PBV maps were calculated from three-dimensional CT-angiographic (3D-CTA) data sets. Imaging was performed on a flat detector, C-arm CT. Groups of response were classified according to the criteria of the response evaluation criteria in solid tumours. Statistically significant differences were determined and Pearson's regression analysis correlated PBV and diameter as parameters of response to treatment.

Results: During 4.91 sessions, median diameter increased 18.18% ($p > 0.05$) and PBV reduced 39.62% ($p > 0.05$). Functional and imaging response per tumour was statistical

significantly different ($p \leq 0.05$). Correlation coefficient was $r = 0.058$. 2/41 tumours showed partial response; 31/41 tumours showed stable disease; and 8/41 tumours showed progressive disease. The highest pre-treatment PBV values were measured in decreasing tumours (206.93 ml l^{-1}), and the lowest values were measured in increasing tumours (60.17 ml l^{-1} ; $p > 0.05$). The lowest values were also measured in lung cancer (53.02 ml l^{-1}) that was significantly different to uterine leiomyosarcoma (103.31 ml l^{-1}) and renal cell cancer (113.14 ml l^{-1} ; $p \leq 0.05$).

Conclusion: Assessment of PBV maps by using 3D-CTA image data is feasible in the clinical routine. PBV shows a stronger response to TPCE treatment than measurement in diameter and should be considered as a response parameter for early detection.

Advances in knowledge: Assessment of PBV using C-arm CT during TPCE is a feasible technique. Assessment of PBV might be useful in assessing response to treatment.

INTRODUCTION

Accountable for 1.4 million deaths, lung cancer is the most deadly type of cancer.¹ The lung is also a common site for metastases of all kinds of cancer with the highest mortality rates.² Treatment is challenging. Radiotherapy and systemic chemotherapy can contain symptoms and extend survival³ but are limited due to intolerance and toxicity.⁴ Ablative methods have shown to be effective⁵ especially for smaller and peripherally located tumours.⁶ The transpulmonary chemoembolization (TPCE) is considered an alternative that allows the treatment of a larger number of tumours

with no risk of pneumothorax⁷ and the treatment of centrally localized tumours. A locally applied chemotherapeutic agent is combined with an application of microspheres and ethiodized oil to occlude tumorous arteries, leading to necrotizing tumour tissue and prolonged drug persistence.⁸

Since this treatment targets the tumour blood supply, common evaluation criteria such as the criteria of the response evaluation criteria in solid tumours (RECIST)⁹ may not be appropriate to assess the response to treatment.¹⁰

That is due to the commonly recognized limitations of basic concepts of tumour measurement that do not detect early functional response.¹¹ Diffusion weighted and dynamic contrast-enhanced MRI are promising techniques that have the ability to assess functional treatment response. Unfortunately, for most clinical situations they are yet impractical due to limits in technology and patient compliance.¹² C-arm CT is a newly introduced technology allowing the acquisition of CT-like images during interventional procedures.

This study presents preliminary experiences with the assessment of parenchymal blood volume (PBV) of pulmonary malignant tumours by using C-arm CT, with a view to its role in detecting early functional response to TPCE and clinical practicability.

METHODS AND MATERIALS

Patients and eligibility criteria

This retrospective analysis was approved by the Frankfurt University Hospital ethics committee. Patients who were assigned to TPCE treatment were included in context of their palliative cancer treatment, after failed systemic chemotherapy or chemotherapy intolerance and no suitability to surgery or ablative treatment options. An interdisciplinary tumour board assigned the patients to TPCE after careful consideration as to “out-of-option” treatment to contain symptoms. All patients were suffering from primary or secondary lung tumours. All types of cancer were allowed. From the pool of TPCE-treated patients, only those patients were included who had TPCE planned by using a three-dimensional CT angiographic (3D-CTA) survey obtained by C-arm CT. Surveys were made before chemoembolization. All patients who had less than two treatment sessions were excluded. The last TPCE defined the end point of the analysis.

Transpulmonary chemoembolization treatment

TPCE was accomplished in 4-week intervals. For patients with multilocal affection, the affected areas were treated in turns based on the load of involvement. Subsequent to regional anaesthesia with 1% mepivacain (Mecain®; Actavis, Langenfeld, Germany), a 5-Fr pigtail catheter (Terumo, Frankfurt, Germany) was inserted into the right femoral vein in Seldinger’s technique and placed into the pulmonary artery supplying the tumour. 3D-CTA surveys of the pulmonary vessel tree were obtained. The post-processed data displayed directly into the interventional room. The obtained 3D-CTA images were studied to exclude arteriovenous (AV) shunts and to find the supposedly best possible position for the application of the chemoembolic agents. The respective intrapulmonary artery supplying the tumour was probed. In cases of peripherally located tumours or tumours infiltrating the chest wall, additional catheter positions were studied. For catheter positions in the descending aorta or the internal thoracic artery, the catheter was inserted into the right femoral artery with a 5-Fr cobra catheter (Terumo). In one treatment session, only one catheter position was used to apply the drugs.

In consideration of prior treatments and cancer type, different chemotherapeutic agents were used, e.g. mitomycin (Medac®, Hamburg, Germany; 5 mg m⁻²), gemcitabin (Gemzar®; Lilly,

Deutschland GmbH, Germany; 1000 mg m⁻²), cisplatin (Hexal®, Holzkirchen, Germany; 25 mg m⁻²) and irinotecan (Hexal; 125 mg m⁻²) alone or in combination. Subsequently, an injection of 60–180 mg of microspheres (Embocept®; Pharmacept, Berlin, Germany) and a maximum of 10 ml of lipiodol (Guerbet, Sulzbach, Germany) for vessel occlusion were applied. Prior to treatment, every patient received 20 mg of dexamethasone (Fortecortin®; Merck, Darmstadt, Germany), 3 mg of granisetron (Kevatril®; Roche Pharma AG, Grenzach-Wyhlen, Germany) and 100 mg of pethidin (Dolantin®; Sanofi-Aventis, Frankfurt, Germany) to reduce nausea and pain. Directly before discharge day, patients received a non-contrast-enhanced CT scan to detect possible complications and displaced thromboembolic material. All sessions were performed ambulatory.

C-arm CT imaging and assessment of parenchymal blood volume

C-arm CT was performed on a multiaxis flat-detector angiographic system (Artis zeego, multi-axis; Siemens AG Healthcare Sector, Forchheim, Germany). The acquisition consisted of two rotations: an initial rotation (mask run) followed by a second rotation after contrast medium (CM) injection (fill run). Data acquisition per run was carried out using the following parameters: acquisition time per run: 6 s, 90 kV, 616 × 480 matrix, projection on 30 × 40-cm flat panel size, 200° total angle, 0.8°/frame, 250 frames total, dose 0.36 µGy/frame. The contrast injection was started manually, immediately after the mask run had been finished, then the C-arm rotated back to start the fill run. The 5 s for back rotation allowed the contrast to distribute through the vessels to fill the lung tumour in an approximately steady state (Figure 1). A total amount of 9 ml of CM (Visipaque® 320; GE Healthcare, Munich, Germany) diluted to 25% (with normal saline) were injected into the pulmonary artery at a rate of 3 ml s⁻¹ using a power injector (Medrad, Indianol, PA). All images were taken at an expiration state of the lung.

PBV post-processing was performed using a dedicated workstation (syngo® XWP; Siemens, Forchheim, Germany). A similar post-processing algorithm was used as described by Zellerhoff

Figure 1. Schematic illustration of the acquisition protocol: obtaining of three-dimensional CT-angiographic images during intervention, when using a C-arm system. (1) Start: mask-run in 6 s, (2) start of contrast medium (CM), after rotating back (5 s) and reaching CM steady state inside the lung parenchyma, (3) start of fill-run (6 s), (4) end of CM-application and data-acquisition. Total amount of CM: 9 ml diluted to 25% injected in 12 s (3 ml s⁻¹). Total scan time approximately 19 s.

Figure 2. Images of a lung tumour situated in the right middle and upper lobe [(f) 60 year old, ICA/non-small-cell lung cancer] during different stages of transpulmonary chemoembolization treatment [first column: (a–d) first session, (e–h) seventh session, (i–m) tenth session]. After an early response and a reduction of the diameter (a–e), tumour progresses under ongoing treatment (e–i). Disease remained stable. The rows show (a, e and i) the assessment of max in-plane diameter and (b–d, f–h, j–l) the procedure of the assessment of parenchymal blood volume (PBV) values. First and second columns show reconstructed fill masks. Third column shows the switching process to the PBV map (fourth column). The arrows denote bone. *regional hyperemia; +catheter artefact.

Table 1. Responses to treatment

Cancer type	Sessions	Sum of PBV/ml l ⁻¹			Sum of diameter (mm)		
		Pre-treatment	Post-treatment	Response	Pre-treatment	Post-treatment	Response
crCA	17	76.02	39.27	PR	31	67	PD
SCCo	2	342.65	126.43	PR	19	18	SD
ICA	11	33.82	33.62	SD	78	62	SD
ICA	2	29.06	82.12	PD	94	96	SD
brCA	8	184.47	173.29	SD	23	53	PD
ICA	2	30.22	2.85	PR	43	41	SD
ICA	3	70.78	87.71	PD	28	33	SD
blCA	3	75.38	41.44	PR	46	38	SD
ICA	8	150.14	108.99	SD	67	63	SD
SCCa	4	228.58	191.76	SD	28	24	SD
ICA	3	60.03	21.61	PR	91	113	PD
cCA	8	397.19	244.41	PR	91	94	SD
brCA	4	52.03	42.38	SD	11	9	SD
SCCo	3	87.31	93.23	SD	50	62	PD
ICA	4	31.30	33.69	SD	43	42	SD
uLMS	5	910.06	242.76	PR	45	44	SD
cCA	4	49.84	42.98	SD	26	25	SD
aS	2	92.22	76.31	SD	8	8	SD
crCA	4	254.53	497.34	PD	54	55	SD
rCA	3	806.69	344.01	PR	97	106	SD
prCA	3	71.37	32.81	PR	36	32	SD

aS, alveolar sarcoma; blCA, urinary bladder cancer metastases; brCA, breast cancer metastases; cCA, cervix cancer metastases; crCA, colorectal cancer metastases; ICA, lung cancer; PBV, parenchymal blood volume; PD, progressive disease; prCA, prostate metastases; rCA, renal cell carcinoma metastases; SCCa, anal squamous cell carcinoma metastases; SCCo, squamous cell carcinoma metastases from oropharynx; SD, stable disease; uLMS, uterine leiomyosarcoma metastases.

When analyzing imaging response to treatment in reference to a patient: no patient (0%) was in state of PR; 17 patients (80.95%) had a SD and 4 patients (19.05%) suffered from PD. When analyzing the alterations of PBV as a response to treatment with a view to a patient, in nine patients (42.86%), it reduced >30%; in nine patients (42.86%), it altered from -30 to 20%; and in three patients (14.29%), it increased >20%. The concordance between both groups in patients was 42.86%.

et al.¹³ In summary, the mask and the fill run were reconstructed and subtracted. An algorithm to segment-out air and bone was applied. The arterial input function value was calculated from an automated histogram analysis of the vascular tree. This arterial input function value was then applied as a scaling factor to obtain the quantitative PBV map that could be visualized with a colour map (Figure 2). In a final step, a smoothing filter was applied to reduce pixel noise. Our algorithm additionally contained a non-rigid motion correction to compensate for motion artefacts between mask and fill acquisition.

Study design

All data, including 3D-CTA data sets, non-contrast-enhanced CT scan images and patients' clinical data, such as age, cancer type and number of TPCE sessions, were obtained from the clinical database.

First, target lesions of all patients were defined and marked in the non-contrast-enhanced CT scans and C-arm CT scans of the first and last TPCE sessions, respectively. The maximum diameter was obtained for every marked lesion, and tumour response was assessed according to the RECIST criteria.¹⁴ Second, PBV maps were calculated from the 3D-CTA data sets as described above. By fusing the reconstructed sets of the C-arm CT scans and PBV maps, PBV values of the target lesions could be assessed and correctly distributed (Figure 2).

The non-parametric Kruskal–Wallis test, including Conover–Iman comparisons, was performed to assess statistically significant differences between the first and last TPCE sessions in diameter and PBV. It was performed to analyze statistically significant differences in PBV when grouped into response in diameter and to assess differences of PBV between cancer types. Response was defined according to the RECIST criteria.¹⁴ To analyze a statistically significant difference between functional and imaging response to

TPCE treatment, non-parametric Wilcoxon matched-pair test was performed. Regression analysis was performed to determine a correlation between the responses to treatment of PBV and tumour diameter. Because of the small number of values of diameter and PBV, median values were chosen to present the middle values, as they are more robust to outliers. All analysis was executed by two of the authors, having more than 3 and 15 years' of experience in diagnostic radiology.

RESULTS

Transpulmonary chemoembolization treatment and imaging response

The analysis included data from 21 patients (15 females and 6 males) between 41 and 77 years of age [mean: 56.77 years; standard deviation: 16.36]. A total of 41 tumours (lung cancer, $n = 8$; breast cancer metastases, $n = 4$; colorectal cancer metastases, $n = 4$; oropharyngeal squamous cell cancer metastases, $n = 3$; bladder cancer metastases, $n = 1$; anal squamous cell cancer metastases, $n = 4$; cervix carcinoma metastases, $n = 6$; uterine leiomyosarcoma metastases, $n = 4$; alveolar sarcoma, $n = 1$; renal cell carcinoma metastases, $n = 5$; and prostate cancer metastases, $n = 1$) were treated and a total of 103 TPCE were performed (mean: 4.91 sessions per patient; standard deviation: 3.69; range: 2–17 sessions; Table 1). In 25 sessions, a chemoperfusion was performed without embolization. Those were the cases where the treatment went over the descending aorta (20 sessions) or the internal thoracic artery (5 sessions).

During the treatment period, the median diameter of all 41 target lesions showed an increase of 18.18%. Median diameter increased from 14.3 mm (range: 3–94 mm) to 16.9 mm (range: 4–113 mm). This change was statistically not significant ($p = 0.912$; Figure 3). As defined by PR, two of the target lesions (4.88%) responded to treatment, 8 target lesions (19.51%) progressed [progressive disease (PD)], and as defined by SD, 31

Figure 3. Box-plot shows median, quartiles and range of diameters of target lesions prior to their first (t1) and last sessions (tx; 4.91 sessions, range: 2–17 sessions). Median diameter increased 18.18% ($p > 0.05$).

Figure 4. Regression line shows the correlation between response to treatment measured by parenchymal blood volume (PBV) and response to treatment measured by diameter $r = 0.0582$ ($p > 0.05$). Grey lines refer to borders of response criteria; PR < -0.3 , progressive disease > 0.2 , stable disease ≥ -0.3 and ≤ 0.2 .

Figure 5. Box-plot shows median, quartiles and range of parenchymal blood volume (PBV) values of target lesions prior to the first (t1) and last sessions (tx; 4.91 sessions, range: 2–17 sessions). Median PBV decreased 39.62% ($p > 0.05$).

target lesions (75.61%) remained stable (Figure 4). When analyzing imaging response to treatment in reference to a patient, no patient (0%) was in a state of PR, 17 patients (80.95%) had SD and 4 patients (19.05%) had PD (Table 1).

Response in parenchymal blood volume

All C-arm CTs were technically successful, and the obtained images could be successfully analyzed. Median pre-treatment PBV of all 41 target lesions was 71.2 ml l^{-1} lung tissue (range: $13.95\text{--}646.75 \text{ ml l}^{-1}$), median post-treatment PBV was 42.99 ml l^{-1} (range: $2.85\text{--}166.55 \text{ ml l}^{-1}$). It decreased by 39.62% during TPCE treatment. This reduction was statistically not significant ($p = 0.11$; Figure 5).

Figure 6. Box-plot shows median, quartiles and range of pre-treatment parenchymal blood volume (PBV) values of target lesions grouped by imaging response. The highest median PBV values were found in responding tumours, the lowest in progressive tumours ($p > 0.05$). PD, progressive disease; SD, stable disease.

The group of responsive target lesions (PR) included lesions with the highest median pre-treatment PBV value (206.93 ml l^{-1} , range: $71.2\text{--}342.65 \text{ ml l}^{-1}$), whereas the group of progressive lesions (PD) included lesions with the lowest median pre-treatment PBV value (60.17 ml l^{-1} , range: $30.82\text{--}97.64 \text{ ml l}^{-1}$). Median PBV of lesions in SD was 73.38 ml l^{-1} (range: $13.95\text{--}646.75 \text{ ml l}^{-1}$). This distribution was statistically not significant ($p > 0.05$) (Figure 6).

Subanalysis revealed that tumours from renal cell cancer showed the highest median pretreatment PBV values (113.14 ml l^{-1} , range: $35.85\text{--}409.44 \text{ ml l}^{-1}$), whereas tumours from lung cancer showed the least PBV values (median: 53.02 ml l^{-1} ; range: $22.87\text{--}137.47 \text{ ml l}^{-1}$). Tumours from uterine leiomyosarcoma had the greatest range (median: 103.31 ml l^{-1} ; range: $56.69\text{--}646.75 \text{ ml l}^{-1}$). The PBV of tumours from lung cancer was significantly different to the PBV of tumours from uterine leiomyosarcoma ($p = 0.02$) and renal cell cancer ($p = 0.037$). Bladder cancer, alveolar sarcoma and prostate cancer had to be excluded from this non-parametric testing, due to the small number of lesions ($n < 2$) (Table 2).

Functional and imaging response

The response (diameter) of the tumours to TPCE treatment was measured between -35.94% and $+133.33\%$ (median: $+1.31\%$). Functionally PBV, the tumours responded to treatment with alterations from $-90.57\text{--}290.4\%$ (median: $+29.93\%$). This imaging and functional responses per tumour were significantly different ($p = 0.036$). They did correlate with a coefficient of $r = 0.0582$ (Figure 5).

Complications

The main complication that occurred during TPCE treatment was due to allergic reactions to CM or the injected chemotherapeutics. After one treatment session, one patient developed a transient flushing. The patient was discharged the same day after symptomatic treatment. Hospitalization was not necessary. No further complications occurred. No patient suffered from pulmonary haemorrhage or femoral aneurysm. No cardiac failure or pneumothorax occurred. No dislodgement of the embolic agent could be detected.

DISCUSSION

Our analysis shows that it is possible to obtain PBV maps during the interventional procedure on a C-arm system by using the acquisition protocol of 3D-CTA imaging that applies CM directly into the pulmonary artery. The protocol is quick (19 s) and has low risks, and it is possible to integrate into the clinical routine. The amount of 9 ml of CM is acceptable and lower than other acquisition protocols in the assessment of 3D-CTA surveys when using normal CT.¹⁵

Literature indicates that the use of 3D-CTA imaging during intervention for the correct placement of the catheter can be of great importance and can improve therapeutic outcome, especially with local tumour control.¹⁶ That is, for example, by detecting AV shunts or AV malformations.¹⁷ It is beyond dispute that overall survival and quality-of-life measure therapeutic outcome clinically significant.¹⁸ For daily cancer treatment, surrogates that assess an immediate treatment response are needed. Palliative treatment is challenging, and practitioners

Table 2. Pulmonary parenchymal blood volume (PBV) prior to treatment

Cancer type	<i>n</i>	PBV/ml l ⁻¹					Significance
		Median	Minimum	Maximum	q1	q3	
ICA	8	34.47	29.06	115.02	30.49	68.09	<i>a</i>
brCA	4	75.84	52.03	97.64	57.94	92.24	
crCA	4	61.84	35.43	95.43	37.22	91.84	
SCCo	3	56.49	30.82	342.65	30.82	342.65	
blCA	1	75.38	75.38	75.38	–	–	<i>b</i>
SCCa	4	56.71	13.95	101.22	21.02	93.72	
cCA	6	71.68	39.85	115.61	47.34	102.71	
uLMS	4	103.31	56.69	646.75	66.13	513.10	
aS	1	92.22	92.22	92.22	–	–	<i>b</i>
rCA	5	113.14	35.85	409.44	40.39	306.49	
prCA	1	71.37	71.37	71.37	–	–	<i>b</i>
All	41	71.20	13.95	646.75	41.03	98.03	

aS, alveolar sarcoma; blCA, urinary bladder cancer metastases; brCA, breast cancer metastases; cCA, cervix cancer metastases; crCA, colorectal cancer metastases; ICA, lung cancer; prCA, prostate metastases; q1, quartile 1; q3, quartile 3; rCA, renal cell carcinoma metastases; SCCa, anal squamous cell carcinoma metastases; SCCo, squamous cell carcinoma metastases from oropharynx; uLMS, uterine leiomyosarcoma.

^aStatistically significant difference to uLMS and rCA ($p \leq 0.05$).

^bExcluded from testing.

need to respond immediately to changes in patients' sensitivity as well as to treatment response. We found that TPCE treatment affects target lesions functionally as well as anatomically. A larger number of tumours responded in the form of a decrease of PBV than in the form of a decrease of diameter. In synopsis with the finding that a higher number of patients showed >30% reduction in PBV than in diameter, whereas the number of patients progressing/increasing was almost the same in both groups, we would assume that PBV responds to TPCE treatment earlier than diameter. If this was true, the assessment of PBV would comply with the statements of Marcus et al¹⁰ on the requirements for an adequate method to assess response to tumour supply affecting treatments. Whether this response is beneficial to patients' survival or quality of life cannot be stated.

Missing survivability, small number and heterogeneity of the investigated group are of course limits of this report. But third and fourth line palliative cancer treatment homogeneity of the investigated groups is merely impossible. It is an investigative field where we still have to rely on our clinical judgement and our clinical expertise. In our opinion, the statement of survivability in individual palliative treatment is not suitable and furthermore can be misleading. In this state of therapy too many factors are coming together that cannot be properly assessed, even with multivariate analyses. Our proposal for further investigations would be to prospectively assess quality of life of TPCE treatment in comparison with an alternative treatment method or best supportive care.

The quantification of lung tumours by CT imaging techniques is not to be found extensively in the literature. However, Sauter

et al¹⁹ recently published quantitative blood volume values of 24 lung tumours of all different kinds of cancer, and since they used stationary perfusion CT and a comparable algorithm for analysis, their findings might be comparable to ours. Mean blood volume of all tumours was slightly higher in their analysis (8.1/100 ml) than in ours (71.2 ml l⁻¹). That might be due to various reasons. For instance, we used the median as a middle parameter and not the mean value. That is because we found it to be a better representative of the real value, due to the distribution of our data. Another reason could be due to the different kinds of cancer that were included. Our data showed statistically significant differences between cancer types. A further possibility could be due to the treatment that the patients received prior to the beginning of the studies. In both studies, pre-treatment data was not assessed and considered, and according to our findings, a reduction of PBV could occur during interventional cancer treatment. Further investigations and a direct comparison between techniques are needed.

Although it was statistically not significant, tumours that responded with a reduction of diameter had the highest pre-TPCE PBV values, while size progressing tumours had the lowest pre-TPCE PBV values. This distribution could relevantly affect the response to treatment, especially in patients with multilobar affections. One of the limits of local tumour control is that the treatment is local and limited only to a certain number of lesions. In those cases, the interventionist has to decide on which tumours to treat first. If PBV can indicate such response, PBV mapping prior to intervention could be mandatory. Of course, further investigations with displaying survivability, quality of life under regularly short-term assessment of PBV maps, are necessary.

In conclusion, the assessment of PBV maps by using 3D-CTA image data is feasible. PBV shows a stronger response to TPCE treatment than size measurement and can be considered as a response parameter for early detection of treatment response. High PBV values before treatment might indicate a larger response to TPCE treatment and could affect the decision on

which tumour to treat first, especially in patients with multilobar affections.

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