Semiautomatic Whole-lesion Apparent Diffusion Coefficient Assessment for Early Prediction of Liver Tumor Response to Radioembolization

NILS RATHMANN[1], JOHANNES BUDJAN[1], FATINAH MARI[1], ROBERT GRIMM[2], ULRIKE ATTENBERGER[1], MICHAEL KOSTRZEWA[1], MALIHA SADICK[1], STEFAN O. SCHOENBERG[1] and STEFFEN J. DIEHL[1]

[1]*Institute of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim, Medical Faculty Mannheim – Heidelberg University, Mannheim, Germany;*
[2]*Siemens Healthcare GmbH, Erlangen, Germany*

Abstract. *Aim: To evaluate volume-based apparent diffusion coefficient (ADC_{VOL}) values for early prediction of therapy response after radioembolization (RE) of primary and secondary liver malignancies using a semiautomatic, image analysis software prototype. Patients and Methods: In a retrospective analysis, 74 target lesions were assessed in terms of therapy response 1 month after RE using magnetic resonance imaging. Changes of the diameter of the target lesions, the mean ADC value in a representative single-slice region of interest (ADC_{ROI}) and mean ADC_{VOL} were correlated. Results: The median progression-free interval (PFI) of patients overall was 3.5±5.9 months. PFI in patients with an ADC_{VOL} increase was statistically significantly longer than in patients with an ADC_{VOL} decrease (mean PFI=6.5 vs. 2.5 months; p=0.0374). No correlation between PFI and early changes in lesion diameter or ADC_{ROI} was found. Conclusion: Semiautomatic, software-based ADC volume measurements seem to offer a clinically valuable parameter for early prediction of therapy response in patients after RE.*

Assessing the response to various therapies in clinical oncological trials frequently requires quantitative evaluation of target lesions, most often according to the established Response Evaluation Criteria for Solid Tumors (RECIST) (1). However, it has been shown that these measurements commonly have a high interobserver variability (2, 3). In addition, tumor response is not always accompanied by tumor shrinkage but might exhibit a pseudo-tumor growth (4-6). Reliable, early treatment assessment is, therefore, essential in order to adequately change the therapy regimen in a timely manner if the tumor fails to respond.

As diffusion-weighted imaging (DWI) combined with calculation of the apparent diffusion coefficient (ADC) provides characteristics about tissue cellularity, structure and water content, it is commonly used for pre- and post-therapeutic follow-up (7). Additionally, ADC provides quantified information about tumor cellularity. Several studies have demonstrated a correlation between low ADC values and an ADC increase after therapy as tumor cellularity decreases (8, 9).

As radioembolization (RE) is a defined, one-stage stimulus, possible changes in tumor imaging might be directly associated with therapy response. Thus, the aim of this retrospective study was to assess early therapeutic changes in primary and secondary liver tumors 1 month after RE and to investigate whether the progression-free interval (PFI) correlates better with absolute changes in diameter, a region of interest (ROI)-based ADC analysis (ADC_{ROI}), or volume-based ADC analysis (ADC_{VOL}).

Patients and Methods

The Institutional Ethics Review Board approved the study (2014-810R-MA).

Study cohort. Of 96 patients with primary or secondary liver malignancies being treated with RE from 2010 to August 2014, 23 were excluded because no magnetic resonance imaging (MRI) examination was conducted before or soon after RE and 23 other patients because MRI quality was not sufficient for statistical image analysis, therefore a total of 50 patients (24 females, 26 males) were included in the data analysis. The surveillance period ended on 31

Correspondence to: Nils Rathmann, Institute of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim, Medical Faculty Mannheim – Heidelberg University, Theodor-Kutzer-Ufer 1-3; D-68167 Mannheim, Germany. Tel: +49 6213832276, e-mail: nils.rathmann@umm.de

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January 2015. When the patient history could not be assessed until the end of the surveillance period, that person was declared as being lost to follow-up and the latest date of imaging was used. The following primary tumor entities were included: colorectal carcinoma (n=14), hepatocellular carcinoma (HCC) (n=10), breast cancer (n=7), lung cancer (n=6), cancer of unknown primary (n=3), gastrointestinal stromal tumor (GIST)/sarcoma (n=3), pancreatic cancer (n=2), gastric cancer (n=2), malignant melanoma (n=1), renal cell carcinoma (n=1), and cholangiocellular carcinoma (n=1).

Treatment protocol. One week prior to RE, selective coil embolization of the gastroduodenal artery, the right gastric artery, and the cystic artery (if not resected) was performed. Relevant hepatopulmonary shunting was ruled out in order to avoid radiogenic pneumonitis. When a shunt volume of 10 to 20% was observed, the dose was adjusted. A value above 20% was regarded as a contraindication for RE (10, 11). Further exclusion criteria were: bilirubin >2.0 mg/dl, a fivefold increase in transaminase levels, and an international normalized ratio above 2.0.

Yttrium-90 resin microspheres (^{90}Y-SIR-Spheres; Sirtex Medical, Sydney, Australia) were used for RE. Depending on the site of the metastases and tumor spread, either both liver lobes were treated (n=37) or one lobe (right: n=10; left n=3). No additional injection of embolization material was performed. The mean applied ^{90}Y activity was: right lobe=1.23±0.23 GBq; left lobe=0.71±0.29 GBq.

MRI acquisition. Pre- and post-treatment MRI was performed following a standardized imaging protocol. To ensure homogeneous ADC values, only MRI scans performed on a 1.5 T MR scanner (MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany) or a second-generation 3 T MR scanner with TrueForm magnet design (MAGNETOM Skyra; Siemens Healthcare) with DWI images acquired in free breathing with b-values of 50/400/800 s/mm^2 (Avanto: 178×144 matrix, 6 mm slice thickness, 5500 ms repetition time, 78 ms echo time, 90˚ flip angle; Skyra: 192×112 matrix, 5 mm slice thickness, 6400 ms repetition time, 64 ms echo time, and 90˚ flip angle) were included; the publication of Rao *et al*. (12) showed that there is no statistically significant difference in ADC values between the two aforementioned MR scanners. In addition, axial T1-weighted vibe, fat-suppressed (fs) MR sequences were acquired (Avanto: 320×150 matrix, 3 mm slice thickness, 4.83 ms repetition time, 1.71 ms echo time, 10˚ flip angle; Skyra: 320×175 matrix, 3 mm slice thickness, 3.95 ms repetition time, 1.27 ms echo time, 9˚ flip angle) in breath-hold before and after contrast media administration in the arterial, portal venous, and equilibrium phase. Axial T2-weighted half-Fourier acquisition single-shot turbo spin-echo (haste), fs sequences (Avanto: 256×192 matrix, 4 mm slice thickness, 1100 ms repetition time, 118 ms echo time, 129˚ flip angle. Skyra: 384×238 matrix, 4 mm slice thickness, 1200 ms repetition time, 79 ms echo time, 129˚ flip angle) were also acquired in breath-hold. The field-of-view was adjusted according to the patient size.

Assessment of tumor response. PFI was defined as the time interval from RE until tumor progression. Progression was assessed using RECIST 1.1 criteria; for HCC and GIST, modified (m) RECIST criteria were used (13-15): a maximum of two target lesions with a minimum diameter of 10 mm in the pretreatment imaging were chosen as baseline. An increase of more than 20% in diameter or additional local therapy (*e.g*. thermal ablation, transarterial chemoembolization) were considered as progressive disease (PD). Therapy response was defined as stable disease (SD), partial response (PR), or complete response (10). To determine the PFI, all available image modalities, such as computed tomography (CT) and positron-emission tomography-computed tomography (PET CT), were used to scan for possible new lesions in addition to MRI.

For correlation of PFI to diameter, ADC_{ROI}, and ADC_{VOL}, the MRI study at 1 month after RE was compared to that at baseline. Here, the target lesions had to be identified on DWI/ ADC imaging in at least three consecutive images for the patient to be included. Two radiologists analyzed the data in consensus (each with 5 years of experience in radiology).

The largest diameter of the target lesions was measured in contrast-enhanced T1-weighted, vibe, fs images. For ADC_{ROI} analysis, a ROI was drawn around the target lesions in a representative single-slice ADC image and the mean value was compared. The data for both methods were analyzed manually using OsiriX medical imaging software (OsiriX 3.7.1; The OsiriX Foundation; Geneva, Switzerland).

For ADC_{VOL}, the images were transferred to a workstation with an image analysis software prototype for semiautomatic assessment (MR OncoTreat; Siemens Healthcare, Erlangen, Germany): first, the software registered pre- and post-RE images automatically using the T2-weighted images as reference. Afterwards, the registration was verified and, if necessary, manually corrected. Using multiplanar reconstruction, the target lesions were segmented on pre-RE ADC images (Figure 1). The segmentation was then transferred onto the post-RE images and compared voxel-by-voxel. To further verify registration of the pre- and post-RE target lesions, a 3D volume reconstruction was displayed and the voxels were color-encoded to show changes in ADC (Figure 2).

Statistical analysis. Statistical analysis was performed using JMP 11.0 (SAS Institute, Cary, NC, USA). Wilcoxon signed-rank test was performed to identify differences in PFI between the groups generated by three different methods of tumor response assessment: decrease in diameter *vs*. increase in diameter; increase in single-ROI ADC *vs*. decrease in single-ROI ADC (ADC_{ROI}); and increase in whole-lesion ADC *vs*. decrease in whole-lesion ADC (ADC_{VOL}). Two-tailed *p*-values less than 0.05 were considered statistically significant.

Results

The median age of the patients was 66 years (range=43 to 81). The median surveillance period was 6.5 months (mean=9.2 months; range=1 to 42 months). At the end of the surveillance period, two patients were still alive, 25 had died, and 23 had been lost to follow-up. Overall, 74 target lesions were analyzed for each of the three parameters (one target lesion per patient: n=26; two target lesions per patient: n=24; median=1). According to RECIST/mRECIST criteria, the median PFI of the whole patient group was 3.5±5.9 months after RE (range=0 to 26 months). At the end of the surveillance period, PD had been found in 37 patients with a median PFI of 3±5.3 months (mean=5 months; range=0 to 26 months). Of the 37 patients with PD, 17 were due to new lesions in follow-up imaging and three because of the need for additional ablative therapy. All others (n=17) showed an

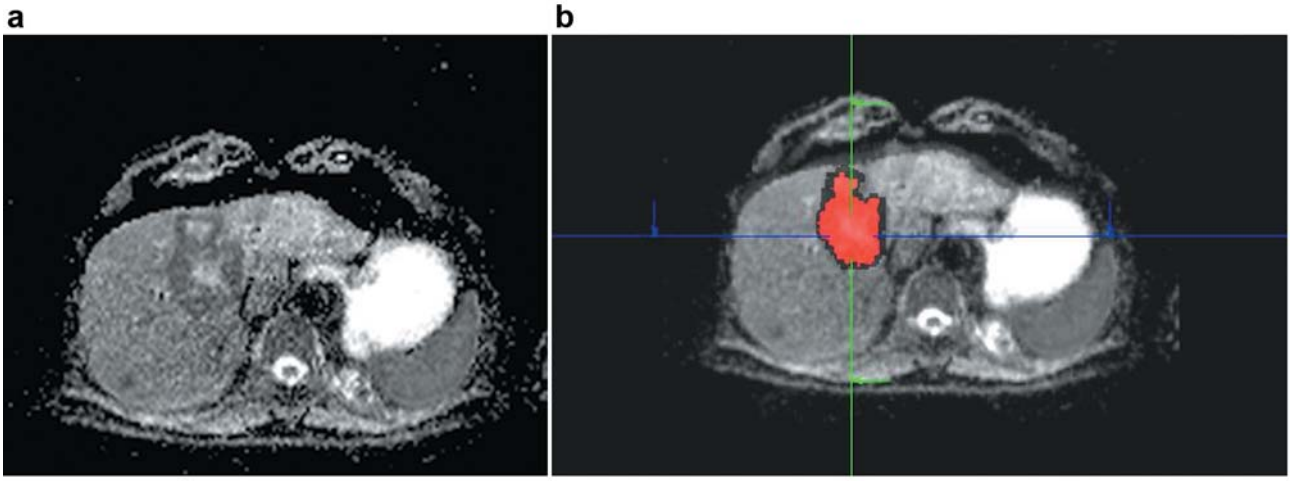

Figure 1. *Tumor segmentation in a patient suffering from colorectal liver metastasis. a: Axial view of target lesion on apparent diffusion coefficient before radioembolization. b: Target lesion segmentation with analysis software in axial view before radioembolization.*

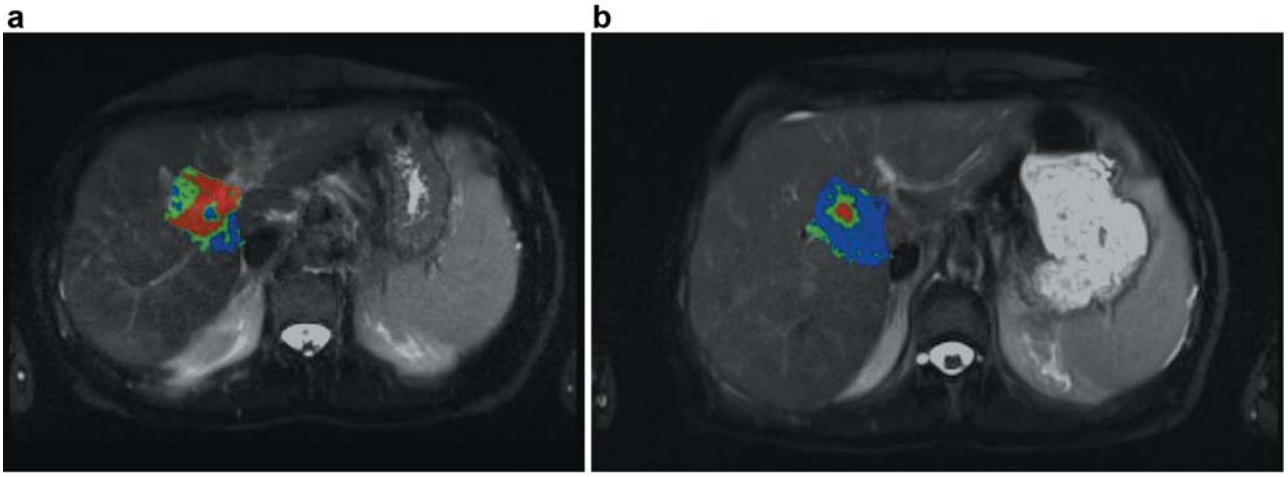

Figure 2. *Voxel-by-voxel comparison of the target lesion segmentation projected on a T2-weighted image. a: Target lesion before radioembolization. b: Target lesion after radioembolization; red: apparent diffusion coefficient (ADC) value >1500; green: 1000 <ADC<1500, blue: ADC<1000×10^{-6} mm^2/s).*

increase in the target lesion in follow-up imaging. Treatment response was found in 13 patients with a median PFI of 6±6.9 months (mean=8.2 months; range=2 to 21 months) until the end of the surveillance period.

The changes in diameter, ADC_{ROI}, and ADC_{VOL} were statistically significant ($p<0.0001$) from baseline to the first follow-up imaging. The median change in diameter was a reduction of 21 mm, of ADC_{ROI} 0.298×10^{-3} mm^2/s, and of ADC_{VOL} 0.181×10^{-3} mm^2/s, respectively. Table I compares the changes in diameter, ADC_{ROI}, and ADC_{VOL} for the groups with a decrease or increase in the first follow-up MRI.

Table II compares the PFI of patients in whom the target lesion diameter, ADC_{ROI}, and ADC_{VOL} had decreased or increased in the first follow-up MRI. The mean PFI of the group with increasing diameter (n=10) did not differ from that of the group with decreasing values (n=40) ($p=0.8545$). Similarly, the PFI for the group with decreasing ADC_{ROI} (n=5), the mean PFI did not differ from that of the group with an increasing ADC_{ROI} ($p=0.8321$). For assessment of ADC_{VOL}, the mean PFI of the group with decreasing values (n=8) was statistically significantly shorter by 4 months than that of the group with increasing values (n=42) ($p=0.0374$).

Table I. *Changes of the target lesion recorded by each method.*

Method	Median change±SD (range)	
	Increase	Decrease
Diameter (%)	7±30 (0-77)	−26±26 (−100-−1)
ADC_{ROI} ($\times10^{-3}$ mm^2/s)	0.316±0.192 (0.026-0.803)	−0.083±0.152 (−0.390-−0.034)
ADC_{VOL} ($\times10^{-3}$ mm^2/s)	0.204±0.105 (0.014-0.525)	−0.096±0.155 (−0.455-−0.001)

SD: Standard deviation; ADC: apparent diffusion coefficient; ROI: region of interest; VOL: volume.

Discussion

For different tumor entities, different approaches for evaluating best response have been published. In this context, diameter measurements as in RECIST and mRECIST are often used but volumetric measurements based on different imaging studies such as CT, MRI, or PET are also employed to assess therapy response. Prasad *et al*. compared uni-dimensional and bi-dimensional evaluation of treatment for liver metastases and compared the results to volumetric measurements in post-contrast CT images. The response results were discordant in 12 of 38 patients using the unidimensional method and in 13 patients using the bidimensional approach. Six patients with PR were rated as having SD with volumetric assessment; two patients rated as having SD showed PR; and four patients with PD were rated as having SD. Thus, due to differing results between volumetric and 2D–measurements, the authors concluded that the value of volumetric measurements for tumor response still needs to be confirmed (16). For assessment of brain metastases, Bonekamp *et al*. evaluated inter- and intraobserver variability in the measurement of diameter and compared it to volumetric measurements (17). The results showed a significant difference ($p<0.001$) between the two methods and a better observer agreement for volumetric measurements. They concluded that volumetric measurements gave reproducible results and seemed to be suitable for oncological follow-up. One drawback of all these studies, however, is the fact that there is no correlation of volumetric or 2D measurements with clinical outcome.

An up-and-coming method of evaluating clinical outcome is the use of ADC measurements. Several studies investigated the feasibility of ADC measurements for tumor response, a correlation between the aggressiveness of cancer and ADC, and, last but not least, the value of ADC for detecting viable tumor areas after therapy (8, 18, 19). In terms of therapy response assessment by ADC, Dudeck *et al*. assessed early response of colorectal liver metastases to RE two days and six weeks after treatment (20). In their study, a statistically significant ($p<0.0001$) inverse correlation between volume decrease and ADC increase was found. They concluded that ADC was able to assess tumor response as early as 2 days after treatment. Another study also concluded that ADC might be capable of predicting of post-treatment colorectal tumor recurrence and tumor response to chemoradiation by pretreatment ADC values, with a sensitivity and specificity of up to 86 and 77% (7).

Table II. *Correlation of changes in the target lesion recorded by each method with the progression-free interval (PFI).*

Method	Mean PFI±SD (range), months		*p*-Value
	Increase	Decrease	
Diameter	5.7±5.0 (2.1 to 9.3)	5.9±6.1 (0 to 16)	0.8545
ADC_{ROI}	5.9±5.8 (1 to 26)	5.6±6.2 (0 to 16)	0.8321
ADC_{VOL}	6.5±6.1 (1 to 26)	2.5±2.0 (0 to 6)	0.0374

SD: Standard deviation; ADC: apparent diffusion coefficient; ROI: region of interest; VOL: volume.

Despite the promising results in tumor assessment using ADC measurements, Heussel *et al*. reported critical aspects concerning the comparison of RECIST and WHO criteria with tumor volume (6). In their study they found clinically relevant differences in tumor staging: 13-17% of the patients were classified differently in PR, SD, and PD by RECIST and WHO criteria. Without being able to clearly identify the underlying reasons, possible effects were discussed. Methodical differences in the assessment of tumor dimensions (1D, 2D, 3D) but also a relatively short median surveillance interval of 56 days were suggested as being responsible. Nevertheless, evaluating response simply by measuring absolute diameter might be limited or even contraindicated depending on the preceding treatment. In ablative therapies, the ablation zone is commonly larger than the primary tumor itself due to necessary safety margins, making measurements of tumor diameter impossible (21). As embolotherapy and RE induce tumor necrosis by hypoxia and radiation, changes in size might only be detected with a

delay (22). Vouche *et al*. analyzed response of HCC to RE with volumetric ADC measurements (23). Again, ADC increased significantly after treatment from a mean ADC of 0.185×10^{-3} mm^2/s (baseline) to 1.093×10^{-3} mm^2/s at 1 month after (p=0.04) and to 0.926×10^{-3} mm^2/s (p=0.03) at 3 months after, but by RECIST failed to show any significant changes.

Therefore, the goal of our study was to compare ADC, on the one hand, and different kind of measurements, on the other, with the clinical outcome. In our study, volumetric assessment of ADC was a valid predictor of tumor response 1 month after RE, correlating to PFI. In addition, our study suggests that the use of 2D measurements is limited for assessing therapy response, as discussed above. Although all but one patient showed a response to RE according to RECIST/mRECIST in our study, no statistically significant differences were observed in PFI (p=0.8321, p=0.8545) in ADC_{ROI} measurements, or diameter assessment with increasing or decreasing values 1 month after RE. Only the volumetric assessment revealed a significant correlation. This finding would suggest that treatment failure could be identified by ADC volumetric measurements at an early stage so that other therapies could be initiated without a loss of time.

It should be noted that the study population was limited to 50 patients over a period of 4 years as only patients for whom imaging quality was sufficient for analyzing diameter, ADC_{ROI}, and ADC_{VOL} were included. Since RE is suggested as a therapy option for progressive liver disease, the patients had problems carrying out the breath-hold sequences. This limited the number of patients with analyzable MRI scans and possible sub-analysis for the different tumor entities. Another limitation is the heterogeneity of tumor histologies, which may not all respond similarly to RE.

In conclusion, semiautomatic, software-based, ADC volumetric measurement in patients after RE showed promising results in identifying patients with early tumor response at 1 month after therapy. Moreover, it could help in identifying patients not responding to RE, allowing the therapy regimen to be changed accordingly at an early stage.

Conflicts of Interest

The Authors state no conflict of interest exists for any aspect of the submitted work.

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