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Original article

Evaluation of the apparent diffusion coefficient in patients with recurrent glioblastoma under treatment with bevacizumab with radiographic pseudoresponse

Timo A. Auer[a,b], Hanns-Christian Breit[a], Federico Marini[d], Mirjam Renovanz[c], Florian Ringel[c], Clemens J. Sommer[e], Marc A. Brockmann[a], Yasemin Tanyildizi[a,*]

[a] University Medical Center, Department of Neuroradiology, Johannes Gutenberg-University Mainz, Langenbeckstr. 1, 55131 Mainz, Germany
[b] University Medical Center–Charité, Department of Radiology, Berlin, Germany
[c] University Medical Center, Department of Neurosurgery, Mainz, Germany
[d] University Medical Center, Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), Mainz, Germany
[e] Institute of Neuropathology, University Medical Center Mainz, Germany

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ABSTRACT

Background. – Response Assessment in Neuro-Oncology Criteria (RANO), are used to asses response to first-line treatment of glioblastoma (GBM). Differentiation between response and pseudoresponse under treatment with Bevacizumab (BVZ) remains challenging. This study evaluates ADC changes in patients with radiographic pseudoresponse under treatment with (BVZ).
Methods. – Patients ($n = 40$) with recurrent GBM under-treatment with BVZ underwent MRI before, two and four months after treatment with BVZ. In patients with radiological pseudoresponse ($n = 11$), ADC analyses were performed. Areas with decreasing T1 contrast enhancement (CE) and FLAIR signal decrease were manually selected and compared to size and position matched healthy contralateral brain parenchyma.
Results. – Histogram based ADC ($10^{-6} \times mm^2/s$) of these patients decreased significantly ($P < 0.005$) from baseline MRI (T1-CE, FLAIR: 1124.9 ± 160.3, 1098.4 ± 226.2, respectively) to 2 months (781.3 ± 110.7, 783.3 ± 103.3) and remained stable during 4 months (777.0 ± 138.5, 784.4 ± 155.4, all mean $\pm$ 1 SD), despite progressive disease. Mean ADC values of the healthy contralateral brain tissue remained stable ($P > 0.05$) (ADC values: baseline: 786.2 ± 110.7, 2 months: 781.1 ± 76.2, 4 months: 804.1 ± 86.2).
Conclusion. – Treatment of GBM with BVZ leads to a decrease of ADC values in areas of pre-treatment T1-CE/FLAIR signal hyperintensity to levels of comparable with normal brain tissue. ADC values remained stable, even when progressive tumor growth was reported.

Introduction

Glioblastoma (GBM) is the most frequent primary malignant brain tumor in adults with an incidence of approximately five cases by 100,000, and a median overall survival of 14 months [1,2]. Standard treatment for patients with GBM involves surgical resection, radiotherapy and chemotherapy (RCT). Chemotherapy with temozolomide (TMZ) is performed concomitantly after surgical resection [2–4]. In patients with recurrent GBM no "standard treatment" exists so far. Besides re-do-surgery, re-radiation and chemotherapy with other alkylating agents such as lomustine, antiangiogenic agents (AG) are being used to treat recurrent GBM [1,2,5]. Bevacizumab (BVZ; Avastin, Roche Diagnostics International AG, Rietkreuz, Switzerland) is one of the antiangiogenic agents targeting vascular endothelial growth factor (VEGF). Whereas BVZ has not been approved for therapy in Europe, it however is still being used in clinical routine as 3rd line therapy, and sometimes in combination with lomustine according to Weathers et al. [6–9]. Due to the highly difficult management of GBM, it has been of great clinical interest to develop response criteria to improve the comparability of response rates between clinical studies with different therapy regimes. Neuro-radiological imaging techniques for instance magnetic resonance imaging (MRI) is commonly used to create valid response criteria.

GBM patients treated with BVZ frequently present with initial radiographic response, although the overall survival rate only shows modest benefits [10,11]. In particular, a significant decrease of tumoral contrast enhancement (CE) after initiating

* Corresponding author.
E-mail address: y.tanyildizi@gmx.net (Y. Tanyildizi).

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BVZ-treatment has been reported, providing response rates up to 60% in phase II studies [11–14]. The discrepancy between remarkable radiographic response and clinical outcome has led to considerable scientific interest. The decrease of CE seems to be a consequence of a normalization of the blood brain barrier (BBB) together with a reduction of vascular permeability, which again results in a reduction of peri-focal edema. This reduction of edema is often followed by an improvement of the patients' clinical status due to a reduction of neurological symptoms. However, there seems to be no relevant reduction of tumor mass [15–17]. This phenomenon has been discussed to be responsible for the discrepancy between impressive radiological response rates and otherwise modest OS (overall survival) benefits [10,11,18,19].

Furthermore, radiographic pseudoresponse (i.e. initial partial or complete response, according to RANO (Response Assessment in Neuro-Oncology) criteria, followed by progressive disease in the next MRI) was frequently detected in GBM patients treated with BVZ. Although RANO criteria are the current standard in response criteria for high-grade glioma, they display their limitations when it comes to radiographic pseudophenomena. Distinguishing between pseudoresponse and real response under BVZ treatment is challenging. According to the RANO working group, alternative evaluation parameters like diffusion weighted imaging (DWI) could be useful to improve assessment of treatment response of GBM, hereby extending the existing RANO criteria.

DWI is based on the physical principles of the Brownian motion of molecules using complex physical processes like the dephasing of spins and their diffusion around inhomogeneous fields [20–22]. Regarding biological tissue, for instance brain parenchyma, diffusivity can be quantified by the apparent diffusion coefficient (ADC) [23–26]. Normally, low ADC values have been reported to represent a higher tumor cellularity, a higher tumor-grade and may even be a marker for a higher tumor activity [25–33]. Higher ADC values, for example can be caused by peritumoral edema [34,35]. Other pathologies, such as necrosis, ischemia, infection or inflammation can lead to ADC value alterations as well [32,36]. Due to heterogonous ADC values in one tumor, mean values in selected tumor areas can miss the accurate reflection of spatial heterogeneity. To decrease the risk of measuring inaccurate ADC values, histogram analyses have been used [26,32]. In the underlying study ADC values in patients with recurrent GBM, under treatment of BVZ with radiographic pseudoresponse and no response were analyzed.

Material and methods

Patients

Patients (mean age: 57.0 years, range: 29–76 years, male: $n = 27$, female: $n = 13$) with GBM in first ($n = 32$), second ($n = 5$) or third relapse ($n = 3$) under therapy with BVZ between October 2004 and May 2016 were retrospectively identified. All patients received standard-of-care treatment, including surgical resection followed by radiation-therapy and adjuvant chemotherapy, according to the EANO-guideline (Stupp's protocol) [3,37]. The adjuvant chemotherapy was either performed as monotherapy with temozolomide (Temodal, Merck & Co, Kenilworth, USA] or as a combined therapy adding Lomustin (CCNU, medac GMBH, Wedel, Germany). All of the patients received BVZ, in relapse situation. Therapy response under BVZ treatment was monitored through MRI (1.5T Magnetom Espree and 3T Magnetom Trio, Siemens AG, Munich, Germany) follow-up examinations. First examination was performed before BVZ administration (baseline MRI) and after two and four months after initiating BVZ therapy (Fig. 1). The study was conducted according to the Declaration of Helsinki in its revised revision.

Radiographic response was analyzed in the 2-months follow-up MR examination, imaging either no response (progressive diseases [PD], stable diseases [SD]) or (pseudo)-response (including partial response [PR] or complete response [CR]) (Fig. 1).

In the latter group, region of interest (ROI), revealing a decrease in T1-CE signal under BVZ treatment from baseline to 2-months follow-up MRI were identified and manually selected (Figs. 2–3). The identified ROIs were manually transferred, matching in size and position, to baseline and 4- months examinations. ADC values (mean, minimum and maximum) were reported (Table 1). Retrospectively, pseudoresponse was unmasked during the 4-months follow up. Furthermore, the selected ROIs, matching in size and position, were transferred to the contralateral, presumably, healthy brain tissue, during baseline, two- and four- months follow-up ADC map. The same method was used to capture ADC values for FLAIR signal increase (Figure 3).

For the first group, progressive diseases were identified through T1 CE/FLAIR–signal increase at the 2-month follow-up MRI. ROI-histogram analysis was done for the new T1 CE/FLAIR signal increase. The selected ROIs, matching in size and position, were manually transferred to the baseline MRI and the corresponding healthy contralateral parenchyma. Some patients of this group showed stable diseases at the 2-month follow-up. For these patients the following MRIs were analyzed, until progressive diseases were found. Histogram analyses was done for the MRI with PD and for the previous MRI, so called "pre MRI". Similar to the patients with pseuodresponse ADC values were reported (Table 2).

Clinical data

The number of BVZ therapy cycles and the corticosteroid (dexamethasone) administration throughout the therapy for each patient was captured and compared between the groups (pseudoresponse vs. no response). The clinical status for each patient was assessed by KPS, (Karnofsky Performance Status) during baseline, 2- and 4-month follow up for patients with pseudoresponse and during baseline, 2-month, pre-MRI and PD MRI for patients with no response (Table 3). The OS for all patients was reported and compared between the two groups (pseuodoresponse vs. no response) [38].

Since molecular-pharmacological mechanisms and adverse effects of BVZ have been discussed to be linked with vascular pathophysiology [39,40], cardiovascular risk factors for every patient were evaluated including hypertension, diabetes mellitus, obesity, former vascular events, hyperlipidemia/hypercholesterinemia and tobacco consumption. As short and long-term vascular pathologies can cause diffusion restriction inside the tumor, white matter lesions (WML) were graded (0–3) according to Fazekas score [41].

Magnetic Resonance Imaging

The MRI protocol included non-enhanced sagittal and axial T1-weighted, axial T2-weighted turbo spin echo, axial T2/FLAIR, T2*weighted gradient echo, contrast-enhanced axial T1-weighted, 3D spoiled gradient echo imaging with coronal and sagittal reconstructions (MP-RAGE) sequences. Gadolinium-DOTA (Dotarem, Guerbet, Villepinte, France) was used as a contrast agent. Diffusion weighted images (DWI) were obtained with echo time/repetition time = 80–135 ms/4–10 s, section thickness = 5 mm with 1 mm intersection gap by using a monopolar spin-echo preparation. Apparent diffusion coefficient (ADC) images were calculated from acquired DW images with b-value 1000 s/mm^2 and b-value 0 s/mm^2 images.

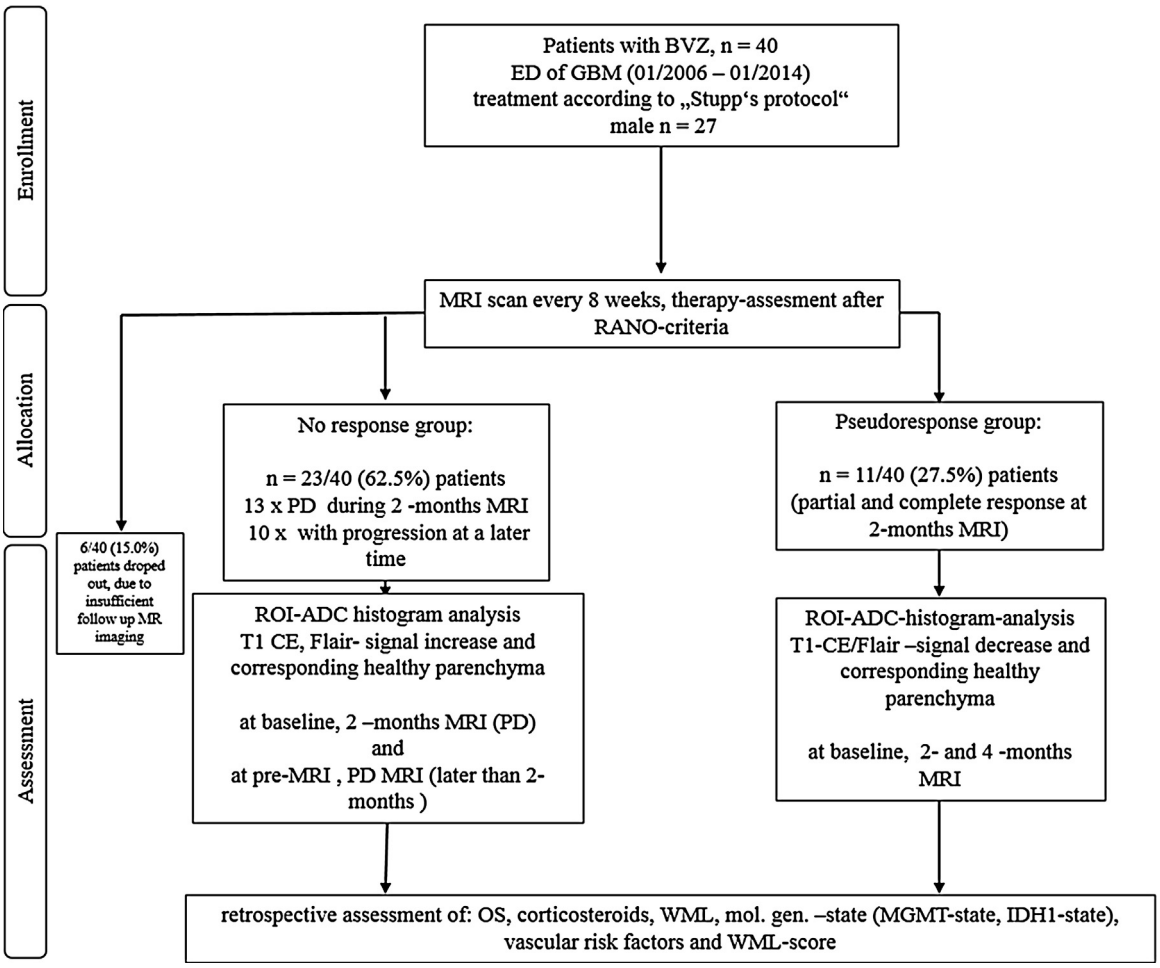

Fig. 1. Flow-chart: enrollment, allocation and assessment.

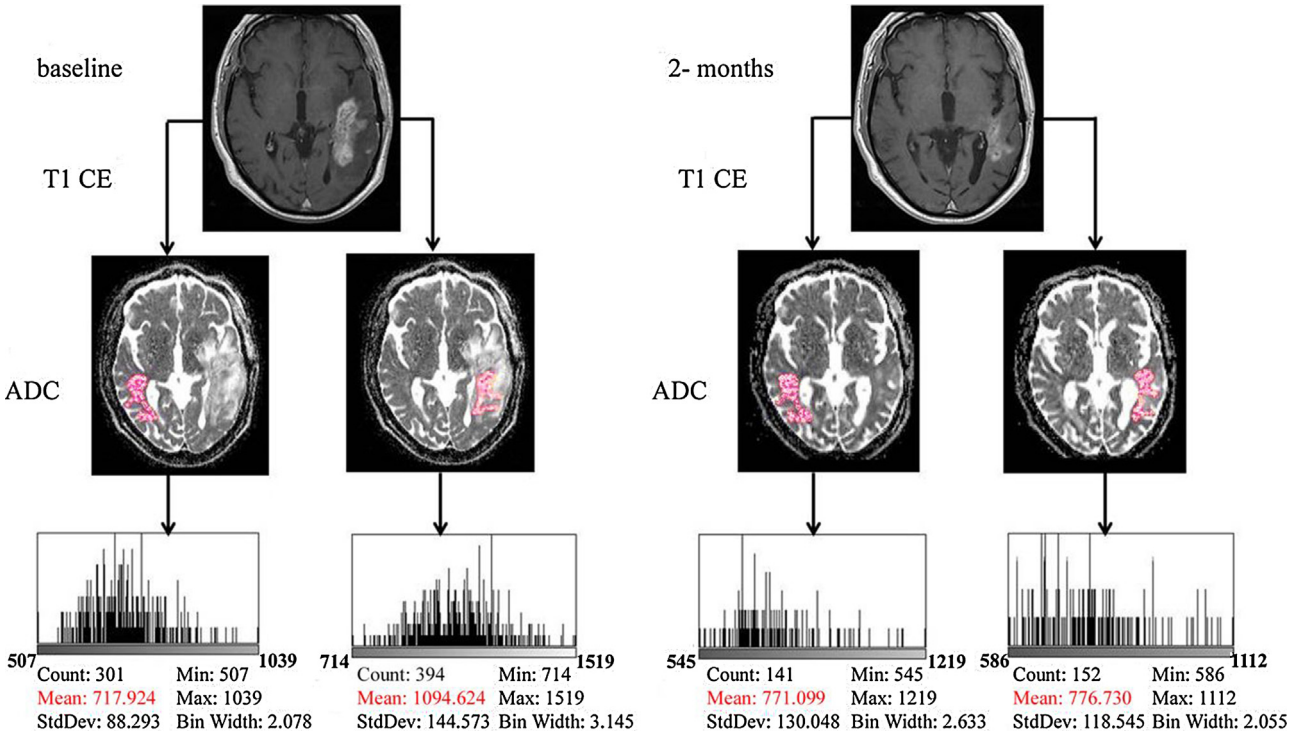

Fig. 2. ADC-histogram-analysis at baseline and 2-month follow-up: contralateral size and position matched healthy brain parenchyma, T1 CE signal decrease.

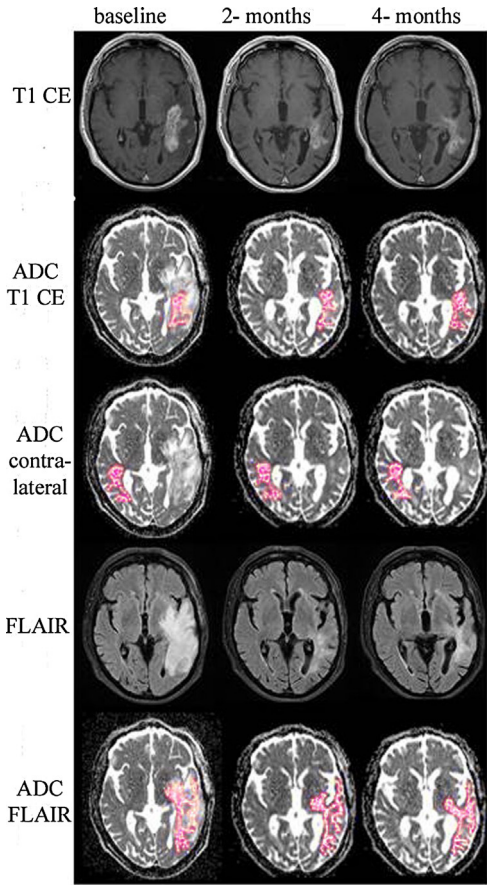

Fig. 3. ROI acquisition during baseline and 2- and 4-month follow-up: T1 CE signal-decrease; size and position matched contralateral healthy brain; FLAIR signal decrease.

Histogram Analyses

The images were analyzed with the ConVis DICOM (Digital Imaging and Communications in Medicine) viewer (conVIs GmbH & Co. KG, Mainz, Germany). For ADC-histograms analyses, original DICOM data (16 bit) was transferred to "image j" (public domain, Wayne Rasband/NIH). ADC-values (mm^2/s) were calculated automatically.

Statistical analyses

All statistical analyses were performed using SPSS Software (IBM; New York, USA). For the statistical results of the proportional distributions, contingency tables were used. All values, unless indicated otherwise, were provided as mean ± SD. Histograms and Plots indicated that normal distributions should not be assumed for metric parameters. Consequently, non-parametric tests were performed. Differentiations between mean ADC-values were analyzed with the non-parametric Kruskal-Wallis test and the Mann–Whitney U test with a Bonferroni-Holm correction for paired tests when necessary. The level of significance was calculated by means of the chi-square-test (χ^2-test) and Pearson's test was performed to evaluate associations between categorical variables. For exploring correlation between categorical and metric parameters, linear regression analyses were performed. We set our significance level at $\alpha = 0.05$. Boxplots were designed with the help of Graph Pad PRISM (Graph Pad Software, Inc.).

Results

Eleven out of 40 patients (27%) could be identified during the 2-month follow up examination with radiographic response according to RANO criteria. The other 29 patients (72% %) did not reveal radiographic response (SD and/or PD) according to RANO criteria. At the 4-month follow-up MR examination, all of the eleven patients (100%) diagnosed with initial response under BVZ showed progressive disease, hereby uncovering a pseudoresponse. Four of these eleven patients were rated PD due to T1-CE and FLAIR-signal increase (36%), three showed an isolated increase of T1-CE (27%), three showed an isolated increase of the T2/FLAIR-signal (27%) and one patient (9%) showed both signs of progress plus a new distant lesion.

Out of the 29 patients with no response at 2-month follow-up, 6 patients dropped out of the study, due to insufficient follow-up data. Out of the 23, 13 showed progressive diseases at the 2-month follow up, 10 showed stable diseases, followed by progressive diseases at a later follow-up examination. Results are displayed in Table 2.

Pseudoresponse group

Measurements of ADC values in areas of tumor, with a reduction of T1 contrast enhancement under BVZ therapy

In all patients with pseudoresponse, the mean (± SD) ADC value (10^{-6}x mm^2/s) of the histogram analyses was evaluated at baseline, 2- and 4-month follow-up MRI. All results are displayed in Table 1. Box-plot analyses for mean ADC values during baseline, 2- and 4-month are provided in Fig. 4. Briefly, mean ADC value was 1124.9 ± 160.3 at the baseline examination (range: 802.3–1352.8), 781.2 ± 110.7 at 2-month follow-up (range: 673.5–1010.7) and 777.0 ± 138.5 at the 4-month follow-up of (range: 571.4–1210.7). Thus, a significant ($P < 0.05$) decrease of the mean ADC value from baseline to 2-month follow- up was detected. No significant changes of ADC values were observed between the 2- and the 4-month control (Table 1, Fig. 4).

Measurements of ADC values in areas of tumor, with a reduction of FLAIR-signal under BVZ therapy

Mean ADC value during baseline examination of 1098.4 ± 226.2 (range: 772.5–1414.9), during 2-month follow-up of 783.3 ± 103.3 (range: 712.3–1003.0) and during 4-month follow-up of 784.4 ± 155.4 (range: 533.5–1007.9) were captured.

A significant ($P < 0.05$) decrease of the mean ADC value from baseline to 2-month could be detected in all patients. Mean ADC values between 2- and 4-month revealed no significant alteration (Table 1, Fig. 4).

Measurements of ADC values for size and position matched areas of the contralateral presumably healthy brain tissue

In the contralateral healthy brain parenchyma, the ADC values revealed no significant alteration between baseline (786.2 ± 110.7; range: 683.4–1394.1), 2- (788.1 ± 76.2; range: 679.1–916.3) and 4-months (804.1 ± 86.2; range: 692.0–997.8).

Furthermore, while the mean ADC values of pre-treatment tumor area decreased from baseline to 2-month follow up for the areas of the tumor with T1 CE/FLAIR signal increase, an adjustment to the mean ADC values of the normal brain tissue could be observed, revealing no significant difference between the mean ADC values of T1-CE/Flair signal decrease and the contralateral size and position matched presumably healthy brain (Table 1, Fig. 4).

Table 1
Descriptive data for ADC-values: T1 CE, contralateral, size and position matched, healthy brain parenchyma and FLAIR signal during baseline, 2-month and 4-month follow-up examination.

Pseudoresponse group $n = 11$	baseline ADC value (10^{-6}x mm^2/s)	2- months ADC value (10^{-6}x mm^2/s)	4-months ADC value (10^{-6}x mm^2/s)
T1-CE	1124.9 ± 160.3[a] 802.3–1352.8	781.3 ± 110.7 673.5–1010.7	777.0 ± 138.5 571.4–1210.7
Contralateral healthy parenchyma	786.2 ± 110.7 683.4–1394.1	788.1 ± 76.2 679.1–916.3	804.1 ± 86.2 692.0–997.8
FLAIR	1098.4 ± 226.2[a] 772.5–1414.9	783.3 ± 103.3 712.3–1003.0	784.4 ± 155.4 533.5–1007.9

[a] Significant difference to 2- months MRI.

Table 2
Descriptive data for ADC-values: T1 CE, contralateral, size and position matched, healthy brain parenchyma and FLAIR signal during time of progression and pre MRI.

No response group $n = 23$	ADC value (10^{-6}x mm^2/s)	*P*-value	ProgressionADC value(10^{-6}x mm^2/s)
$n = 13$	Baseline MRI		2-months Progression
T1-CE	925.6 ± 148.2[a] 746–1196	0.003	746.3 ± 161.3 532–930
Contralateral healthy parenchyma	764.6 ± 72.5 678–879	0.570	727.6 ± 111.9 548–868
FLAIR	981.0 ± 197.1 703–1273	0.387	867.6 ± 232.6 523–1271
$n = 10$	pre MRI		Progression (at a later time than 2 months)
T1-CE	986.0 ± 96.5 837–1056	0.089	829.0 ± 161.3 733–983
Contralateral healthy parenchyma	798.6 ± 89.9 698–887	0.545	788 .5 ± 93.0 657–864
FLAIR	811.25 ± 111.1 696–962	0.483	856.5 ± 148.3 731–1051

[a] Significant difference to 2-months MRI.

No response group

Measurements of ADC values in areas of tumor, with new T1 CE and FLAIR-signal increase under BVZ therapy

Between baseline and 2-month follow-up a significant difference was observed between the mean ADC values for T1 CE, at the same time no significant differences for FLAIR signal increase and for the contralateral healthy brain parenchyma was found. All results are displayed in Table 2.

Evaluated clinical data

The reported clinical data displayed in Table 3 showed no significant differences between patients with radiological pseudoresponse and no response. In patients with radiographic pseudoresponse mean KPS at baseline MRI was 73.6, which increased after BVZ administration to 75.5 at 2-month follow up. However, during progression (4-month follow-up) a decrease of 7 percentage points to 68.5 was reported. Comparing the KPS between the two groups, the KPS decreases from 69.6 points to 66.0 during BVZ treatment for the patients with no response. In conclusion, no significant difference could be reported (Table 3).

The evaluation of the genetic profile showed a positive methylated MGMT-state for nine (22%) patients, whereas in 19 (47%) patients the MGMT-gen was unmethylated and in twelve (30%) patients no MGMT-state could be found in the database. In 16 patients (40%) IDH1-state was positive, in one patient (2.5%) IDH1 was mutated, while in 23 patients (57%) no data were available. No correlation between a positive MGMT-state ($P = 0.356$) and/or a positive IDH1-state ($P = 0.478$) and radiographic pseudoresponse was found (Table 3).

The evaluation of the vascular risk profile for each patient is displayed in Table 2. WML graded according to Fazekas revealed minor or no signs of WML in 80% of the patients (Fazekas grade 0: 40%; Fazekas grade 1: 40%), while 10% of the patients were presented with Fazekas grade 2 and grade 3, respectively (Table 3).

Discussion

According to European Association of Neuro-Oncology (EANO) guidelines, standard treatment for newly diagnosed GBM involves surgical resection and RCT. In the relapse situation, due to the absence of therapy standards for each patient, further individual therapy has to be planned. Besides re-do-surgery, re-radiation, chemotherapy agents, antiangiogenic drugs such as BVZ are taken into account [3,37]. However, while BVZ is licensed in the USA and an accepted 2nd line therapy, in European countries, BVZ treatment is not approved. Former studies have reported a significant radiographic response rate in more than 25% and up to 60% after initiation of BVZ treatment, resulting in a modest survival rate [10,11]. The remarkable radiographic responses, followed by a discrepancy in clinical benefits, have led to considerable scientific interest.

Although highly standardized RANO criteria for evaluating therapy assessment have been well established, it is still challenging to discriminate between radiographic response and pseudoresponse under BVZ treatment, as both are initially presented with a reduction of T1 CE and FLAIR signal. Different approaches have been

Table 3
Clinical data for all patients and divided into sub-cohorts (no response and radiographic pseudoresponse).

Characteristics	Patients receiving BVZ ($n = 40$)	Pseudo-responder ($n = 11$)	Non-responder ($n = 29$)	P-value
Age (in years)	57 ± 11.6	61.5 ± 8.5	55.9 ± 12.4	0.46
	29–76	50–74	29–76	
Gender				
Male	27	8	19	0.66
Female	13	3	10	
Overall survival (in months)	13.2 ± 13.4	14.0 ± 4.5	12.5 ± 15.8	0.31
	9–24	5–69	5–69	
KPS (%)				
At the beginning of BVZ treatment	76.3 ± 10.3	73.6 ± 14.4	69.6 ± 9.9	0.27
	60–100	60–100	60–100	
At 2-month FU			0.15	
	54.5 ± 14.8	75.5 ± 8.2	66.0 ± 8.5	
at 4-month FU	10–90	70–90	50–90	0.14
At the end of BVZ treatment	68.5 ± 8.7.	59.0 ± 15.0		
		50–80	5–90	
		50.0 ± 13.4		
		30–70		
No. of BVZ cycles	11.9 ± 8.4	14.8 ± 7.6	9.0 ± 8.6	0.1
	2–33	5–33	2–31	
MGMT-Status				
Methylated	9	4	5	0.76
Unmethylated	19	5	14	
No data	12	2	10	0.41
IDH1-Status				
Wildtype pos.	16	6	10	
Wildtype mut.	1	0	1	
No data	23	5	18	
Patients (n) receiving Corticosteroids	23	8	15	0.46
Patients (n) with vascular risk factors				
Hypertension	23	7	13	0.57
Diabetes mellitus	4	2	2	0.29
Obesity	4	2	2	0.29
Former vascular event	8	3	5	0.48
Hyperlipidemia/Hypercholesterolemia	7	2	2	0.49
Tobacco consumption (n) (mean pack years, range)	11	3	8	0.98
	25.2	41.5	25.1	
	5–50	30–50	5–50	
White matter lesions graded according to	0:16	0:03	0:13	
Fazekas (grades: 0-III)	I:16	I: 5	I:11	
	II:4	II: 3	II: 1	0.54
	III:4	III: 0	III: 4	

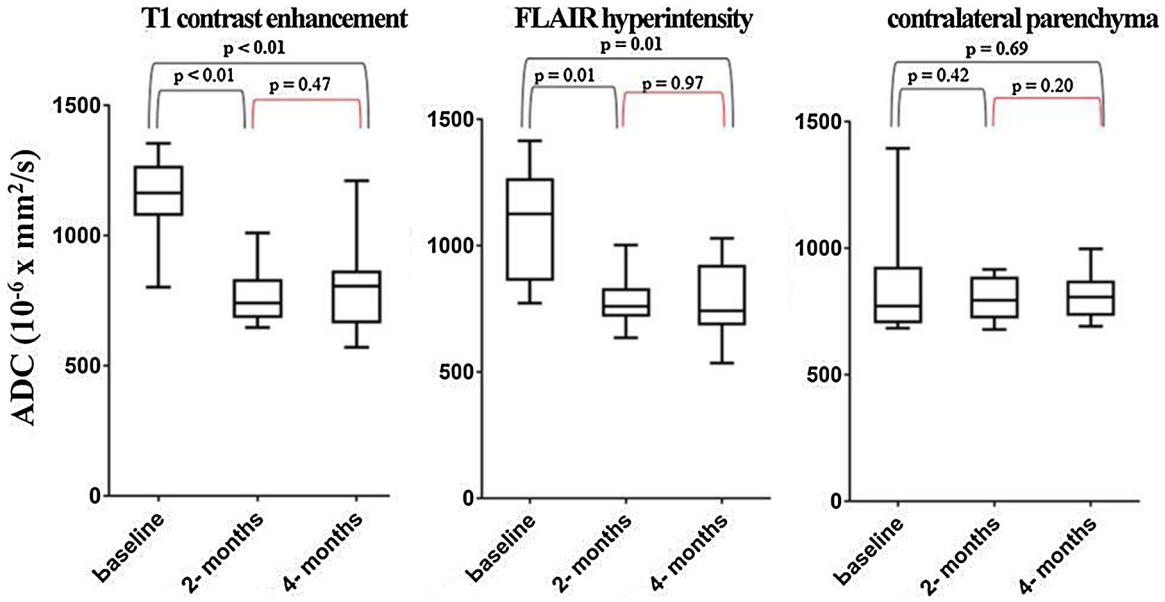

Fig. 4. Boxplots at baseline, 2- months and 4-month follow-up: T1-CE-signal decrease, contralateral size and position matched healthy brain parenchyma and FLAIR-signal decrease.

recommended by the RANO working group to improve diagnostic accuracy of radiographic pseudoresponse, including alternative techniques such as DWI, MR-spectroscopy and MR-perfusion.

DWI has been reported in several studies to reliably improve assessment of malignant gliomas [25,26,28,33,42,43]. Histogram-analyses of ADC-maps have been used to determine progression free survival (PFS] in newly diagnosed GBM, unmasking infiltrative patterns of tumor growth by identifying real tumor progression [26,44–47]. Furthermore, BVZ has been discussed to normalize the permeability of peritumoral blood vessels, [12,13,48] resulting in a reduction of tumoral contrast enhancement as well as a decrease of peritumoral edema [48–50]. The underlying study evaluates ADC values during this normalization.

To our best knowledge, it is the first study evaluating ADC-value alterations in recurrent GBM under BVZ treatment with radiographic pseudoresponse and no radiographic response, comparing this to the contralateral normal parenchyma. In line with the literature approximately 30% of the patients in this study show a radiographic pseudoresponse. The evaluated ADC values within the selected areas of T1 CE and FLAIR signal hyperintensity, show a significant decrease from baseline MRI to 2- months MRI. After first time BVZ treatment, a normalization of the ADC values to the level of healthy brain parenchyma can be observed, followed by stable ADC values during the 4-month MRI. ADC values for the contralateral parenchyma remain stable during the period of observation. The patients with no response to first time BVZ administration show a significant decrease for the ADC values in new T1 CE areas, but in contrast to the patients with pseudoresponse, no significant decrease for the ADC values in new FLAIR signal hyperintensities can be observed.

BVZ has been discussed to normalize the permeability of peritumoral blood vessels, with this leading to a reduction of peritumoral edema. The normalization of the peritumoral blood vessels might be imaged through a decrease of ADC values, especially in FLAIR sequences. As patients with no response and progressive diseases do not show a significant decrease of ADC values in selected FLAIR hyperintensities, less edema reduction is be observed for patients with no response, leading to no better clinical state after first time BVZ administration. This theory is emphasized through an initial better tendency for the KPS during (pseudo−) response, while the KPS decreases in points during progression for both groups. Levels of cortisol administration were captured, showing no significant differences between both groups, excluding a bias induced by different edema reductions through cortisol.

The current issue to uncover and predict specific sub-cohorts of recurrent GBMs, in the early stages of BVZ administration, who will show a therapy response under BVZ treatment, remain still unclear. The aim is to predict valid clinical endpoints (OS, PFS) and stratify the survival of malignant brain tumors through MRI. Further approaches have to be made to establish these reliable, predictive MRI biomarkers. It has been discussed, that ADC-values could play a key role in this future prospective. With the help of volume based multiparametric imaging with integrated ADC-maps, it might be possible to identify and classify histopathological different regions within the tumor [51]. Emphasized by the current literature, reporting new possible advances of antiangiogenic therapies in several GBM sub-cohorts [8,9,52], further studies are needed in order to evaluate GBM therapy assessment under BVZ treatment, using multi-parametric imaging.

Limitations of the study

The limitations of our study are (1) retrospective character of the analysis, (2) small number of patients, (3) observation of a heterogeneous patient samples at several stages (2nd, 3rd recurrences) of the disease, (4) not all clinical and sociodemographic data could be obtained due to the retrospective character, (5) an investigator-bias cannot be excluded, (6) missing multiparametric imaging.

Conclusion

Pseudoresponse in patients with recurrent GBM after first time BVZ is associated with a normalization of the mean ADC values to the level of normal brain parenchyma within areas of T1 CE and Flair signal decrease. ADC values remain stable in these patients treated with BVZ, even though progressive tumor growth is reported. During the (pseudo)- response an increasing KPS can be observed, indicating better clinical conditions. BVZ might induce a significant reduction of the edema, leading to better clinical conditions. Similar normalization of the ADC values can be observed within new T1 CE, for patients with PD after first time BVZ administration. In contrast to this, no significant decrease of ADC values within areas of FLAIR signal hyperintensity can be found. This is indicating less edema reduction through BVZ administration in patients with no response and PD after first time BVZ treatment, emphasized by decreasing KPS points during PD.

However, no prediction regarding radiographic pseudoresponse and determination of valid clinical endpoints, like OS can be provided only from ADC analyses. For this reason, further studies are needed to evaluate GBM therapy assessment under BVZ treatment focusing on the molecular mechanism BVZ is inducing, imaged through MRI.

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Disclosure of interest

The authors declare that they have no competing interest.

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