Advantages of high \( b \)-value diffusion-weighted imaging to diagnose pseudo-responses in patients with recurrent glioma after bevacizumab treatment

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**Abstract**

Background: The diagnosis of pseudo-responses after bevacizumab treatment is difficult. Because diffusion-weighted imaging (DWI) is associated with cell density, it may facilitate the differentiation between true- and pseudo-responses. Furthermore, as high \( b \)-value DWI is even more sensitive to diffusion, it has been reported to be diagnostically useful in various clinical settings.

**Materials and methods:** Between September 2008 and May 2011, 10 patients (5 males, 5 females; age range 6–65 years) with recurrent glioma were treated with bevacizumab. All underwent pre- and post-treatment MRI including T2- or FLAIR imaging, post-gadolinium contrast T1-weighted imaging, and DWI with \( b=1000 \) and \( b=4000 \). Response rates were evaluated by MacDonald- and by response assessment in neuro-oncology working group (RANO) criteria. We also assessed the response rate by calculating the size of high intensity areas using high \( b \)-value diffusion-weighted criteria. Prognostic factors were evaluated using Kaplan–Meier survival curves (log-rank test).

**Results:** It was easier to identify pseudo-responses with RANO- than MacDonald criteria, however the reduction of edema by bevacizumab rendered the early diagnosis of tumor progression difficult by RANO criteria. In some patients with recurrent glioma treated with bevacizumab, high \( b \)-value diffusion-weighted criteria did, while MacDonald- and RANO criteria did not identify pseudo-responses at an early point after the start of therapy.

**Discussion and conclusion:** High \( b \)-value DWI reflects cell density more accurately than regular \( b \)-value DWI. Our findings suggest that in patients with recurrent glioma, high \( b \)-value diffusion-weighted criteria are useful for the differentiation between pseudo- and true responses to treatment with bevacizumab.

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1. Introduction

Glioblastoma is the most common malignant primary neoplasm of the central nervous system. Despite aggressive treatment, it almost always recurs with fatal consequences. As vascular endothe-

\[ \text{tial growth factor (VEGF)} \] and its receptors are highly expressed in glioblastoma, VEGF may constitute an important molecular target in its treatment. VEGF increases vascular permeability and contributes to contrast enhancement and the peritumoral edema associated with these tumors. Anti-angiogenic agents, especially those targeting VEGF such as bevacizumab, can significantly reduce vascular permeability. This results in diminution of the enhanced lesion irrespective of changes in the tumor size. Therefore, it is very difficult to determine the responder status of glioma patients treated with bevacizumab on conventional MR images and some tumors thought to have responded to bevacizumab therapy exhibit progression without manifesting an increase in the size of the gadolinium-enhanced tumor. This phenomenon, defined as a “pseudo-response”, has been observed immediately after the start of treatment and renders the accurate assessment of a true tumor response difficult [1–3]. Emerging evidence of survival prolongation in patients who responded to bevacizumab [4] suggests that it exerts antitumor effects. Reliable means to assess the treatment response and the progression of these tumors addressed with anti-

angiogenic agents must be developed.

The response assessment based on neuro-oncology working group (RANO) criteria takes into account increases in the enhanced tumor size, the T2/FLAIR high size, the dose of corticosteroids, and clinical symptoms. Using RANO criteria, it may be possible to iden-

tify tumor progression after treatment with bevacizumab because post-treatment the non-enhanced tumor area tends to increase without an increase in the size of the enhanced tumor. This may
also be reflected by an increase in the size of the T2/FLAIR high-intense lesion. On the other hand, as treatment with bevacizumab may reduce the size of brain edema, it may be difficult to distinguish between true- and pseudo-response at an early point after treatment with bevacizumab.

As the apparent diffusion coefficient (ADC) calculated from diffusion-weighted (DW) images is associated with tumorcellularity [5], it is considered an important biomarker of cancer [6,7]. The ADC has also been used to assess the response of brain tumors to therapy [7] and to predict survival in patients with newly diagnosed glioblastoma [8]. DWI studies at higher diffusion gradient strength (b-values) have been used for the diagnosis of acute stroke [9], the assessment of lesion-to-normal contrast in neurodegenerative diseases [10], the prediction of the glioma grade [11], and for the differentiation between glioblastoma and malignant lymphoma [12]. The aim of this study was to evaluate whether RANO criteria and DW imaging including high b-value DW (HBDW) imaging could assess the pseudo-response after treatment with bevacizumab. Here we show that HBDW imaging may represent a useful tool for the diagnosis of pseudo-responses in glioblastoma patients treated with bevacizumab.

2. Materials and methods

2.1. Patients and MR imaging

Between September 2008 and May 2011, 10 patients (5 males, 5 females; age range 6–65 years) with recurrent glioma were treated with bevacizumab in our institutions. Recurrence before the administration of bevacizumab was defined by MacDonald criteria [13].

All MRI studies were performed on a 3 T superconducting system (Signa Excite HD 3.0T; GE Medical Systems, Milwaukee, WI, USA). All patients underwent pre- and post-treatment magnetic resonance (MR) imaging including T2- (TR 4800 ms, TE 100 ms, echo train length 18, field-of-view (FOV) 22 cm × 22 cm, matrix size 512 × 320/2NEX, section thickness 6 mm, intersection gap 1.0 mm, 1 acquisition) or FLAIR imaging (TR 10,000 ms, TE 140.0 ms, inversion recovery time 2400.0 ms, FOV 22 cm × 22 cm, matrix size 288 × 160/1NEX, section thickness 6 mm, intersection gap 1.0 mm, 2 acquisitions), gadolinium-enhanced T1-weighted imaging (TR 450 ms, TE 18 ms, FOV 22 cm × 22 cm, matrix size 256 × 192/1NEX, section thickness 6 mm, intersection gap 1.0 mm, 2 acquisitions), and DW imaging at b = 1000 and b = 4000 s/mm. The parameters at b=1000 and b=4000 DWI were: 8-channel phased array head coil, TR 5000 ms, TE 66.2 ms (b=1000) and TR 5000 ms and TE 96.4 ms (b=4000), NEX 1, FOV 220, slice thickness 6 mm, gap 1.0 mm, number of slices 20, data acquisition matrix 128 × 128, scan time 20 s (b=1000) and 40 s (b=4000).

2.2. Response after treatment with bevacizumab

The response rate was determined using 3 different methods. Under MacDonald criteria [13], the enhanced tumor size was calculated and defined as complete response (CR = disappearance of all enhanced target lesions), partial response (PR = a 50% decrease from the baseline), stable disease (SD = neither PR nor progressive disease (PD) criteria are met), PD (a 25% increase over the smallest sum recorded or the appearance of new lesions), the clinical assessment and corticosteroid dose were also recorded. Under the criteria of the response assessment in neuro-oncology (RANO) working group [2], factors such as enhanced tumor size, T2/FLAIR high size, dose of corticosteroids, and clinical symptoms were taken into account. At visual inspection, HBDW (b=4000) imaging was superior to regular b-value based (b=1000) DW imaging for the assessment of size changes of high-intense lesions. Therefore, under the third method we calculated the size of the high-intense lesion on HBDW images using its two dimensional measurements and established HBDW criteria where CR = disappearance of all high intensity lesions on HBDW images, PR = a 50% decrease from the baseline of high intensity lesions observed on HBDW images, SD = neither PR nor PD criteria are met, PD = a 25% increase over the smallest sum recorded or the appearance of new DW high lesions on HBDW images.

2.3. Statistical analysis

Statistical analyses were with PRISM version 5.0 (GraphPad Software Inc., La Jolla, CA, USA). The survival time of patients with recurrent glioma that was measured from the time of initial treatment with bevacizumab to the time of death or last follow-up. To evaluate prognostic values we performed Kaplan–Meier survival analysis (log-rank test) that incorporated the response to bevacizumab based on MacDonald–, RANO–, or HBDW criteria.

3. Results

Table 1 presents a summary of our patients. Their age ranged from 6 to 65 years (mean 42.5 years, median 40 years). Based on MacDonald criteria, the initial response rate was CR, n = 4; PR, n = 4; SD, n = 1; PD, n = 1; under RANO criteria it was CR, n = 2; PR, n = 3; SD, n = 3; PD, n = 2, and under HBDW criteria, the initial response rate was PR, n = 3; SD, n = 3; PD, n = 4 patients.

After bevacizumab administration, the enhanced lesion disappeared in 5 tumors and based on MacDonald criteria CR was recorded. In 3 patients there was a decrease in the size of both the T2/FLAIR- and the HBDW high intense lesion; based on RANO and HBDW criteria, PR was recorded (Fig. 1, case 5). These patients are currently alive without recurrence and their treatment with bevacizumab continues.

In some patients the high intensity lesion on T2/FLAIR- and HBDW images increased (Fig. 2, case 1). They were categorized as PD under RANO or HBDW criteria. After continued treatment with bevacizumab, they were recorded as PD. In some patients there was a decrease in the size of the T2/FLAIR high intense lesion after one cycle of bevacizumab. However, in 2 patients the high intense lesion became larger on HBDW images (Fig. 3, case 2) and based on RANO criteria PD was recorded after the continuation of bevacizumab treatment.

We performed Kaplan–Meier survival analysis based on the response rate determined by MacDonald–, RANO–, and HBDW criteria. Under MacDonald criteria we observed no statistical difference between CR/PR- and SD/PD patients (Fig. 4A). Under RANO criteria there was a statistical difference between CR/PR- and SD/PD patients (p = 0.0153, Fig. 4B) and under HBDW criteria the difference was more obvious and CR/PR patients survived longer (p = 0.0152, Fig. 4C).

4. Discussion

Our study documents that in patients with recurrent glioblastoma, DWI is the superior imaging technique for the diagnosis of pseudo-responses and that HBDW imaging is particularly advantageous. We also show that RANO is superior to MacDonald criteria because the size of non-enhanced tumors increases after bevacizumab treatment. On the other hand, as the strong effect of bevacizumab against brain edema may produce a decrease in the T2/FLAIR high intense area, this may hide the extension of the tumor area shown as an increase in the T2/FLAIR high intense area. HBDW imaging clearly demonstrated the extent of the tumor area at an early time point after the start of treatment with bevacizumab.
Table 1  
Summary of patients treated with bevacizumab.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Disease</th>
<th>After 1 cycle</th>
<th>After 2–5 cycles</th>
<th>Overall survival</th>
</tr>
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<tr>
<td></td>
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<td>RANO</td>
<td>HBDW</td>
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<tr>
<td>1</td>
<td>47</td>
<td>F</td>
<td>Glioblastoma rec.</td>
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<td>PD</td>
<td>PD</td>
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<tr>
<td>2</td>
<td>42</td>
<td>F</td>
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<td>PR</td>
<td>PD</td>
<td>PD</td>
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<tr>
<td>3</td>
<td>65</td>
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<td>Glioblastoma rec.</td>
<td>SD</td>
<td>SD</td>
<td>PD</td>
</tr>
<tr>
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</tr>
<tr>
<td>5</td>
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<td>Glioblastoma rec.</td>
<td>CR</td>
<td>CR</td>
<td>PR</td>
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<tr>
<td>6</td>
<td>43</td>
<td>M</td>
<td>Anaplastic astrocytoma rec.</td>
<td>CR</td>
<td>CR</td>
<td>PR</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>F</td>
<td>Anaplastic astrocytoma rec.</td>
<td>PR</td>
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<td>PD</td>
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<td>8</td>
<td>13</td>
<td>F</td>
<td>PNET rec.</td>
<td>PR</td>
<td>PD</td>
<td>PD</td>
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<tr>
<td>9</td>
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<td>M</td>
<td>Pontine glioma rec.</td>
<td>CR</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>F</td>
<td>Pontine glioma rec.</td>
<td>PR</td>
<td>SD</td>
<td>SD</td>
</tr>
</tbody>
</table>

RANO, response assessment in neuro-oncology working group; HBDW, high b-value diffusion-weighted; rec., recurrence; PNET, primitive neuroectodermal tumor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

There is an apparent increase in the tendency for infiltrating tumor progression after anti-angiogenic treatment; this is discernible on T2-weighted- and FLAIR images [14]. This may be attributable to the recruitment of existing blood vessels. Under RANO criteria, the most recent response criteria for glioma, T2/FLAIR images are taken into account [2]. However, other factors, e.g. post-irradiation- and/or postoperative changes, chemotherapy, tumor infiltration, and tumor-induced edema, may produce changes on T2-weighted- or FLAIR images, pointing to the need for clear response criteria.

Newer imaging techniques such as PET, MR spectroscopy, and perfusion- and diffusion-weighted imaging that provide functional information may be more reliable in the assessment of tumor activity during anti-angiogenic treatment [2]. Tumor-cell density decreases if treatment is effective. On the other hand, ineffective treatment or tumor recurrence results in increased tumor-cell density and the size of the high cell density area increases due to an increase in the tumor size [7].

Ours is the first documentation that HBDW (b=4000) imaging at MRI more effectively distinguishes between pseudo- and true responses than other MRI techniques including standard b=1000 DW imaging. HBDW imaging has been found to be useful for the diagnosis of acute infarction [9], degenerative diseases [10], for glioma grading [11], and for the differentiation between glioblastoma and malignant lymphoma [12]. Preclinical studies using HBDW support our findings that HBDW may be useful for the early detection of responses to chemotherapy [15]. At HBDW there is more contrast at the tissues of interest than at regular b value imaging [16] and it has been reported that there are slow- and fast diffusion components that correspond with intra- and extracellular...

Fig. 1. This 37-year-old man with glioblastoma underwent radical surgery and radiotherapy with concomitant and adjuvant chemotherapy with temozolomide. Gadolinium (Gd)-enhanced T1-weighted- (A) and FLAIR images (B), DW images at b=1000 s/mm² (DWI1000) (C) and at b=4000 DWI (DWI4000) (D) were acquired before treatment with bevacizumab. Gd-enhanced T1-weighted images showed a markedly decrease in the enhanced lesion (E). On FLAIR images (F), DWI1000 (G), and DWI4000 (H) the high intensity area was decreased. At present, 6 months post-treatment, there has been no tumor recurrence and he continues to receive bevacizumab treatment.
diffusion, respectively [17,18]. Studies on multi-component diffusion in brain tissue demonstrated that the slow component is more sensitive at HBDW than regular b-value DW imaging, suggesting that the ADC based on higher b-values reflects changes in tumor cellularity more accurately [12]. In fact, Doskaliyev et al. [12] found that the ADC is inversely associated with tumor cellularity and that this correlation is stronger with the ADC obtained at HBDW (b=4000) than regular b-value DW (b=1000) imaging.

Calculation of the ADC should also be considered for the assessment of the tumor response. However, the ADC is associated with tumor cellularity but not with the tumor size. A decrease in cellularity after effective treatment would result in an increase in the ADC.

Fig. 2. This 47-year-old woman with glioblastoma underwent radical surgery and radiotherapy with concomitant and adjuvant chemotherapy with temozolomide. Gd-enhanced T1-weighted- (A) and FLAIR images (B) and DWI1000 (C) and DWI4000 (D) were acquired before treatment with bevacizumab. Gd-enhanced T1-weighted images showed a marked decrease in the enhanced lesion (E). On FLAIR images (F) and DWI1000 (G) and DWI4000 (H) the high-intensity area was increased. She died of tumor recurrence 5 months after the first course of bevacizumab.

Fig. 3. This 42-year-old woman with glioblastoma underwent radical surgery and radiotherapy with concomitant and adjuvant chemotherapy with temozolomide. Gd-enhanced T1-weighted- (A) and T2-weighted images (B) and DWI1000 (C) and DWI4000 (D) were acquired before bevacizumab treatment. Gd-enhanced T1-weighted images showed a marked decrease in the enhanced lesion (E). On T2-weighted images we noted a marked decrease in the high intensity area, a decrease in the mass effect, and improvement in the midline shift (F). DWI1000 showed an increase in the high intensity area (G). On DWI4000 there was an obvious increase in the high-intensity area (H). She died of tumor recurrence 3 months after first course of bevacizumab.
However, calculation of the ADC at identical tumor sites before and after treatment is difficult. Moreover, it would be difficult to interpret changes in the ADC without evaluating the size of the tumor. In addition, use of the terms hyper- and hypocellularity instead of decreasing ADC and increasing ADC may be misleading since many pathologies and clinical scenarios affect ADC measurements.

The quantification of diffusion changes has evolved from the mean change in the ADC to a voxel-by-voxel approach termed the functional diffusion map (fDM) [7], a statistical method that prospectively compares heterogeneous ADC maps acquired after the start of therapy with pretreatment ADC maps. The two image data sets are co-registered and computationally analyzed to yield statistical maps of ADC changes as color overlays on anatomical images and to provide scatter plots of ADC changes to determine the tumor response in patients with brain tumors. Such information makes it possible to tailor treatments based on an early imaging biomarker readout in cases where an insufficient response is predicted. The fDM was proposed as an MRI biomarker for the quantification of the early brain tumor response to therapy [19].

Although the fDM approach is promising, technical and clinical challenges must be addressed [20]. First, the proper alignment of sequential images on baseline images is difficult but critical. A significant mass effect from tumor growth or intracranial pressure induced by edema may skew the registration between DW imaging datasets. Suspected tumor regions near gyri, sulci, or the ventricles may return false results due to misregistration effects. The proper choice of the $b$-value used for an accurate estimation of the ADC is an important aspect of fDM implementation that must be addressed. Also, the use of $b$-values greater than 1500 s/mm$^2$ results in a multi-exponential signal decay that may render a single estimate of the ADC inappropriate. Additional studies are necessary to confirm the usefulness of the fDM approach.

Our preliminary study has some limitations. First, we must consider that acute occlusion of the tumor vessels may produce high intensity on DW images. Time-course observations and monitoring of ADC changes may help to identify pseudo-responses. Second, although HBDW ($b$-4000) imaging was superior to regular $b$ value-based ($b$-1000) DW imaging for the assessment of pseudo-response at visual inspection, HBDW imaging had the disadvantage of an inferior signal/noise ratio, and it may be possible to assess pseudo-responses by regular $b$-value DWI. Quantitative analysis that includes the tumor ADC value or the fDM approach is necessary to confirm the advantage of HBDW. In addition, the optimal $b$-value has not been determined. Third, tumors with lower cellularity and tumors with micro-necroses or micro-cysts may not show high intensity on HBDW images. Fourth, in our study the patients' age and the tumor histology were inhomogeneous. Fifth, the 6-mm slice thickness we used may be too high for an accurate assessment of the character of the lesion. Thinner slices may make it possible to characterize the lesions more accurately. Sixth, our study population was small and prospective studies on large patient populations, studies to identify the optimal $b$-value, and studies that include quantitative approach are necessary.

In conclusion, HBDW criteria could identify a pseudo-response earlier than RANO criteria. We presented evidence that HBDW imaging may represent a biomarker in glioma patients subjected to anti-angiogenic therapy.

**Conflict of interest**

None.

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Appendix A. Supplementary data


References


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