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Diffusion restriction associated with bevacizumab treatment in recurrent glial tumors, evaluation of survival with ADC measurement analysis

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Abstract. – OBJECTIVE: Recurrent glial tumors treated with bevacizumab often develop diffusion restriction. In this study, we investigated the diffusion restriction pattern after bevacizumab treatment along with the relationship between apparent diffusion coefficient (ADC) values of regions with diffusion restriction and survival period as there are conflicting results on this relationship.

PATIENTS AND METHODS: We retrospectively identified 24 patients treated with bevacizumab for recurrent glial tumor who had low ADC values after the onset of the treatment. Magnetic resonance imaging (MRI) findings were analyzed for the presence of restricted diffusion, time to onset, location, duration of restriction, and persistence of restriction after cessation of bevacizumab treatment. A retrospective study was performed to investigate the relationship between ADC values obtained at first post-bevacizumab scan and survival periods.

RESULTS: Diffusion restriction appeared 2 to 6 months after the onset of bevacizumab therapy and persisted up to 24 months while on bevacizumab. The restricted diffusion persisted up to 6 months after cessation of bevacizumab. Our results showed that there is a negative correlation between ADC values and progression free survival as well as overall survival. Patients having diffusion restriction areas with lower ADC values after the initiation of bevacizumab treatment, are found to have increased overall and progression free survival ($p<0.05$).

CONCLUSIONS: In patients with recurrent glial tumor treated with bevacizumab, diffusion restriction can be observed and the ADC values obtained from these areas at first post-bevacizumab MRI scan correlate with progression free and overall survival with the worst survival seen in patients with higher ADC values which therefore can be considered as an imaging marker that can predict the prognosis.

Key Words:
Bevacizumab, Magnetic resonance ımaging, Glial tumor, Diffusion.

Introduction

Gliomas are the most common primary brain tumors in adults with a median survival of 15 months[1]. Standart treatment for newly diagnosed glioblastoma is surgical debulking followed by radiotherapy and temozolomide (TMZ) with additional maintenance TMZ[1]. At the time of disease recurrence, few treatment options are available and bevacizumab (BEV) is one of them.

High-grade gliomas express a high degree of vascular endothelial growth factor (VEGF) which makes them very vascular tumors. BEV, a recombinant monoclonal antibody, is an anti-VEGF agent that blocks its binding to the receptors on endothelial cells[2,3]. Studies have shown that it improves progression-free survival (PFS)[4]. However, it has no effect on overall survival (OS)[5,6]. VEGF inhibitors, such as BEV, reduce and normalize the permeability of the blood-brain barrier resulting in decreased contrast enhancement and peritumoral edema on imaging. Therefore, evaluating the treatment response can cause confusion. Other multiparametric magnetic resonance imaging (MRI) sequences should also be included in determining the response to BEV.

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Diffusion-weighted imaging (DWI) is an advanced MRI technique that measures the motion of water, which might enable evaluation of BEV response as this parameter is not related to contrast enhancement[7,8]. Low signal intensity on apparent diffusion coefficient (ADC) maps refers to increased diffusion restriction. Some patients, when given BEV, develop prominent diffusion restriction. It has been shown that these areas can be seen due to either treatment related coagulative necrosis or tumor recurrence[9-14]. It has also been reported that the ADC values of necrosis areas are significantly lower than the tumor recurrence areas[15,16]. However, there are conflicting results about the relationship between the ADC values of regions with diffusion restriction and survival. In a study[9,17] that was based on serial MRI scans, it has been reported that lesions with progressing BEV related diffusion restriction are associated with worst overall survival whereas lesions with stable diffusion restriction have longer survival periods. In another study[18], it has been shown that homogeneous dark signal on ADC maps at initial follow-up scan, which suggests BEV induced necrosis, is associated with longer survival. However, ADC value- PFS relation was not investigated in that study. We hereby, investigated the diffusion restriction pattern associated with bevacizumab treatment in recurrent glial tumors along with the relationship between ADC values of regions with diffusion restriction obtained at first post-bevacizumab scan and OS as well as PFS. We aimed to find an imaging marker that can predict prognosis right after the initiation of the bevacizumab treatment of the glial tumors as selection of the patient group that could benefit from the chosen therapy is of great importance.

Patients and Methods

Study Population

The study was conducted according to the Declaration of Helsinki with the approval of the Hospital Ethics Committee (2021-06/1220). Informed consent was obtained from all individual participants included in the study. We performed a retrospective study on patients who underwent brain MRI after starting treatment with BEV for recurrent gliomas in our hospital, which is an oncology center. MR imaging studies and medical records of patients aged 18-65 years who received BEV treatment for residual or recurrent brain tumors, were screened. Thirty-one patients with pathologically confirmed initial glioma who had BEV treatment after the assessment of the recurrence based on clinical data and MRI findings were retrospectively assessed by using our clinical PACS system to determine whether diffusion-restricted lesions developed following treatment onset. Restricted diffusion means regions with low ADC values, and it was observed in 28 patients. Patients with missing MR images or treatment records and patients with low-quality diffusion-weighted images were excluded from the study. Two of these patients were excluded from our study because they did not have follow-up MRI scans in our hospital. One of the patients had low-quality diffusion weighted images. One other patient had missing treatment records (Figure 1). All of the 24 patients were followed up with residual or recurrent brain tumor, had used BEV during their treatment course and had at least one follow-up MRI study while on BEV treatment. The death dates of the patients were recorded as well as the demographic findings. OS was calculated from the day BEV started to the date of death whereas PFS was calculated from the day BEV started to the date of progression.

MRI Analysis and Image Interpretation

MRI was performed on a 1.5T Signa Excite HDx scanner (GE Healthcare, Waukesha, WI, USA) equipped with an eight-channel head coil. Our imaging protocol included pre- and post gadolinium 3D volumetric T1-weighted inversion recovery spoiled gradient-recalled sequences, T2-weighted FLAIR sequence, axial, sagittal and coronal T2-weighted fast spin-echo sequence, and a spin-echo EPI (echo-planar imaging) DWI sequence, ADC images were calculated from acquired DWI data with b=1000 s/mm^2 and b=0 s/mm^2. The ADC values were obtained with the largest ROI that fits within the diffusion restriction area.

Restricted diffusion defines high signal on diffusion-weighted imaging (DWI) and low signal on apparent diffusion coefficient (ADC) images. Serial MR scans were obtained at 2 to 3-month intervals. MRIs were analyzed for presence of restricted diffusion, time to onset of diffusion restriction after the start of BEV treatment, location, duration of restriction, and persistence of restriction after cessation of BEV treatment.

Two radiologists with 4 years of experience (M.F.G.) and 18 years of experience (B.S.) who were blinded to the clinical status and outcome, interpreted the images in consensus. ADC measurements were obtained by using region-of-in-

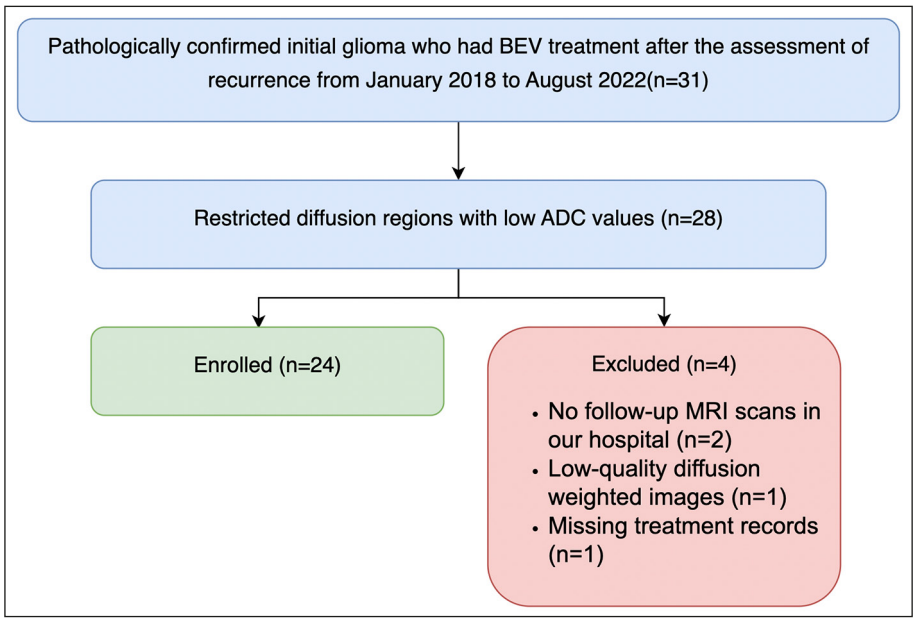

Figure 1. Flow diagram showing the study recruitment process.

terest (ROI) analysis and quantitative ADC values were obtained by placing the largest circular ROI within the region of diffusion abnormality on every axial ADC slice. The mean ADC value was recorded for all scan dates for each patient.

Statistical Analysis

Data analysis was performed with statistical software SPSS, version 20.0, (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to check for data normality. Categorical variables were expressed as number (n) and percentage (%), while continuous variables were reported as mean, standard deviation (SD), or median values depending on the distribution. When testing continuous variables, the Independent Samples *t*-test was used if the test's parametric assumptions were fulfilled. Otherwise, the Mann-Whitney U test was used. Statistical significance was set at $p<0.05$. ROC curve was drawn for ADC values. Spearman and Pearson analyses were performed to explore correlation between ADC values and survival time, both after BEV initiation and progression free survival. Kaplan-Meier method was used to evaluate 1-year survival according to ADC threshold.

Results

The cohort consisted of 9 female (37.5%) and 15 male (62.5%) patients with a mean age of 44 (range 24 to 65 years). Tumor histology included 21 glioblastoma (87.5%), one anaplastic oligodendroglioma (4.2%), two grade 3 astrocytoma (8.3%). All patients received radiation, temozolomide therapy and BEV at tumor recurrence (100%). The area of diffusion restriction was adjacent to the lateral ventricle in 12 patients (50%), at centrum semiovale in 7 patients (29.2%), at corona radiata in 4 (16.7%) patients, at corpus callosum in one patient (4.2%).

Diffusion restriction appeared 2 to 6 months after the onset of BEV therapy and persisted up to 24 months while on Bevacizumab. The restricted diffusion persisted up to 6 months after cessation of Bevacizumab. Thirteen patients died under BEV therapy.

ADC values according to one-year survival were statistically significant ($p<0.05$). Our results showed negative correlation between ADC values and survival after BEV initiation ($p<0.05$, r=-0.855) (Figure 2). Similarly, significant negative correlation was present between ADCs and progression free survival ($p<0.05$, r=-0.856) (Figure 3). Patients with higher ADC values after the initiation of BEV treatment are found to have decreased overall survival ($p<0.05$) (Figures 4 and 5).

ROC analysis revealed an ADC threshold of 0.697×10^{-3} mm^2/s (AUC: 95%) according to one-year survival after BEV therapy initiation (Figure 6). Tumor grade based statistical analyses were insignificant regarding ADC values, survi-

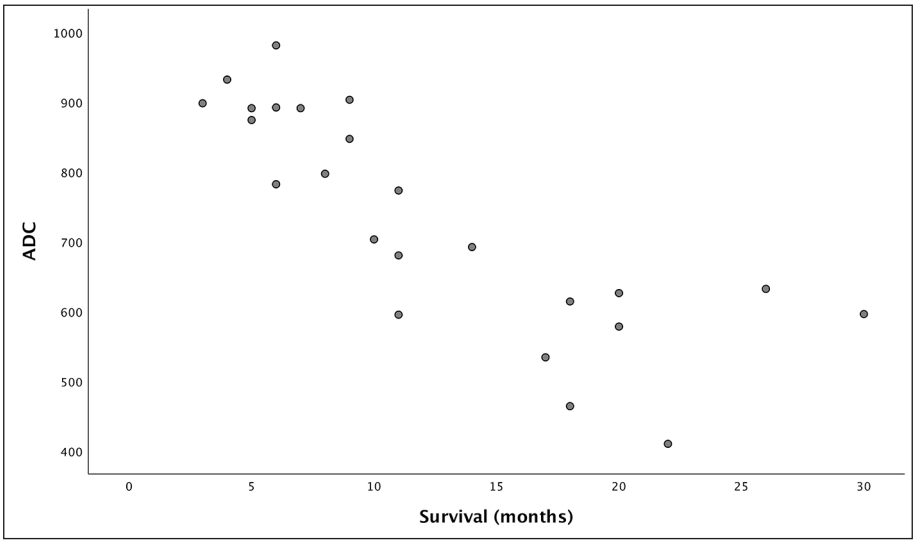

Figure 2. Scatter plot of ADC and survival time after BEV therapy initiation.

val after BEV initiation and progression free survival (p=0.059, p=0.244 and p=0.249, respectively). Survival analysis showed that patients with lower ADC values than the threshold, had longer survival periods (Figure 7).

Discussion

Our results suggest that in patients with recurrent glial tumor treated with BEV, diffusion restriction can be observed. Besides, ADC values obtained from these areas at first post-BEV MRI scan correlate with progression free and overall survival with the worst survival seen in patients with higher ADC values which therefore can be considered as an imaging marker that can predict the prognosis. Moreover, our survival analysis revealed an ADC threshold of 0.697×10^{-3} mm^2/s, when compared according to one-year survival after BEV therapy initiation with the lower ADC values than the threshold, having longer survival periods. Recognition of diffusion restriction characteristics on first follow-up scan is essential as it has potential to identify the patients who are likely to respond

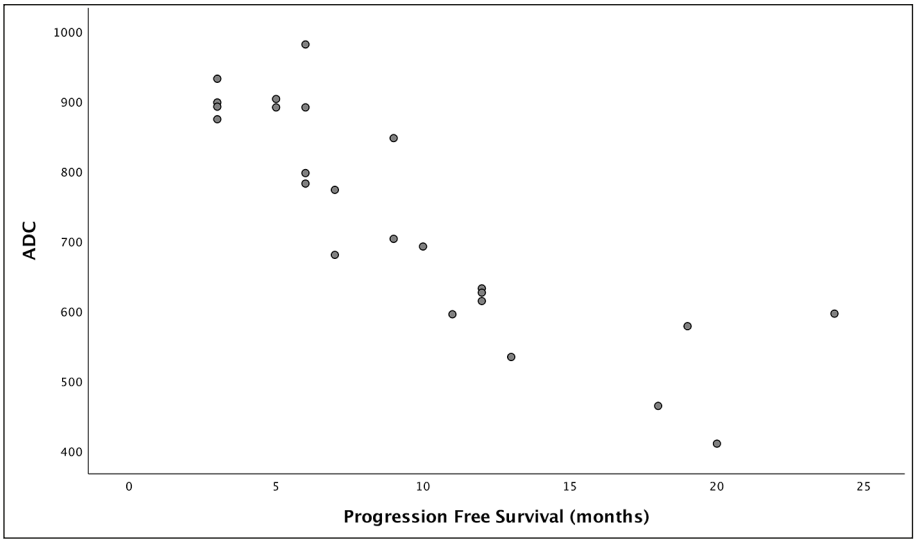

Figure 3. Scatter plot of ADC and progression free survival after BEV therapy initiation.

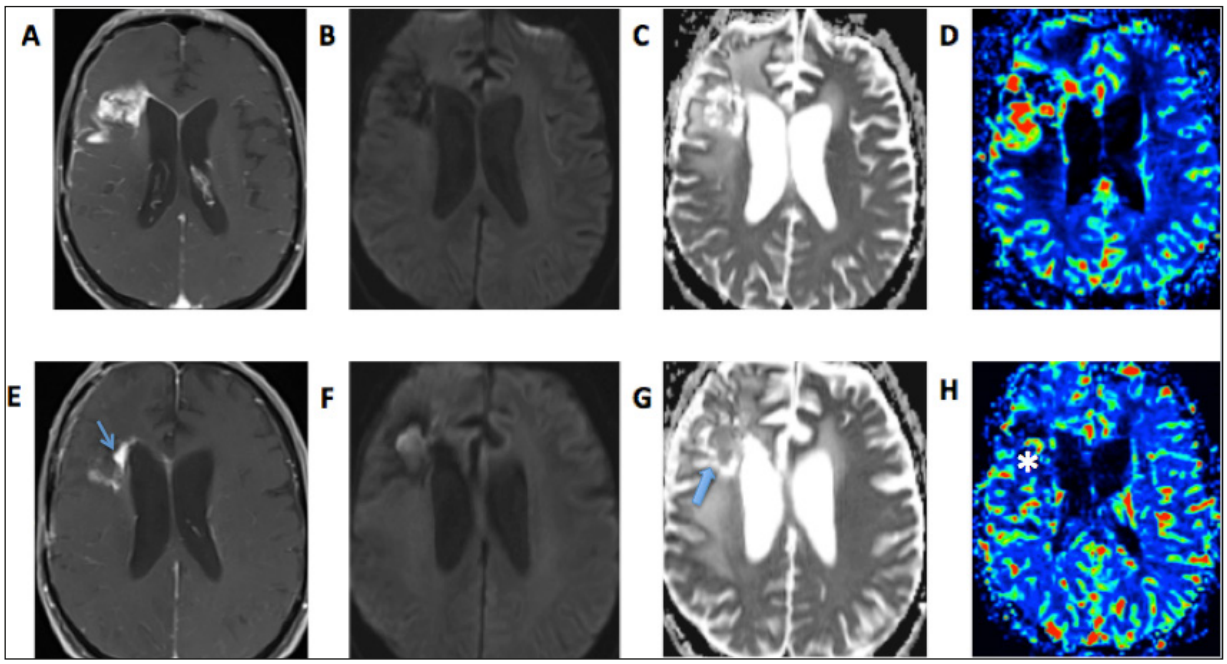

Figure 4. Axial post-contrast T1-weighted (**A**), diffusion-weighted imaging (**B**), ADC (**C**), perfusion imaging (**D**) at pre-BEV scan and corresponding images at first post-BEV scan (**E-H**). Patient had higher ADC values on first post-BEV MRI (block arrow) and expired one month after the first post-BEV scan. Note that the contrast enhancement (arrow) and perfusion decreased after BEV treatment (star).

to BEV treatment and will have longer survival periods eventually.

Recurrent brain tumors treated with BEV often develop diffusion restriction. Previous glioma studies[2,19,20] investigating post-BEV diffusion restriction development have found an inverse correlation between tumor cellularity and ADC[1]. On the other hand, others[9,12,17,19] have stated that these lesions may be BEV-induced necrosis areas as bevacizumab binds to VEGF and prevents the development of blood vessels therefore producing an ischemic environment that eventually ends up with necrosis. Nguyen et al[17] performed postmortem examination on 6 patients and their findings suggest that regions of diffusion restriction are diffusion-restricted coagulative necrosis. Rieger et al[3] hypothesized that such regions result from BEV-induced chronic hypoxia. Some studies[9] tried to enlighten this issue by investigating serial MRI scans. They characterized the changes of the restricted- diffusion lesions and their relation with survival[9]. However, survival prediction based on serial MRI scans can result in loss of time.

The main purpose of this study was to investigate the relationship between ADC values of regions with diffusion restriction on first follow-up MRI scan and survival periods as there are conflicting publications on this topic in the literature[3,9,11,14,21-23]. Nguyen et al[17] found that progressing BEV-induced diffusion restriction causes decreased survival in patients with recurrent glioblastoma. However, the study by Mong et al[9] found that patients who demonstrated diffusion restriction following BEV treatment had increased overall survival. Zhang et al[11] found that survival was dependent on the size of the focal lesion. In the current study, we retrospectively analyzed the diffusion restriction seen right after BEV treatment and tried to determine whether ADC values on first post-BEV scan can predict progression-free or overall survival. We especially focused on first post- BEV MRI scan to determine the survival relationship with ADC as this patient group has relative short life-span and it would be more effective if we could make an assessment as soon as possible. Furthermore, these lesions will eventually develop viable tumor and therefore BEV-induced diffusion restriction if present would best be demonstrated at first follow-up scan.

We also analyzed the time-dependent changes of these diffusion-restriction areas. In a previous study by Rieger et al[3], the diffusion restriction was detected as early as 4 weeks after the initiation of the BEV treatment. Besides, they found it main-

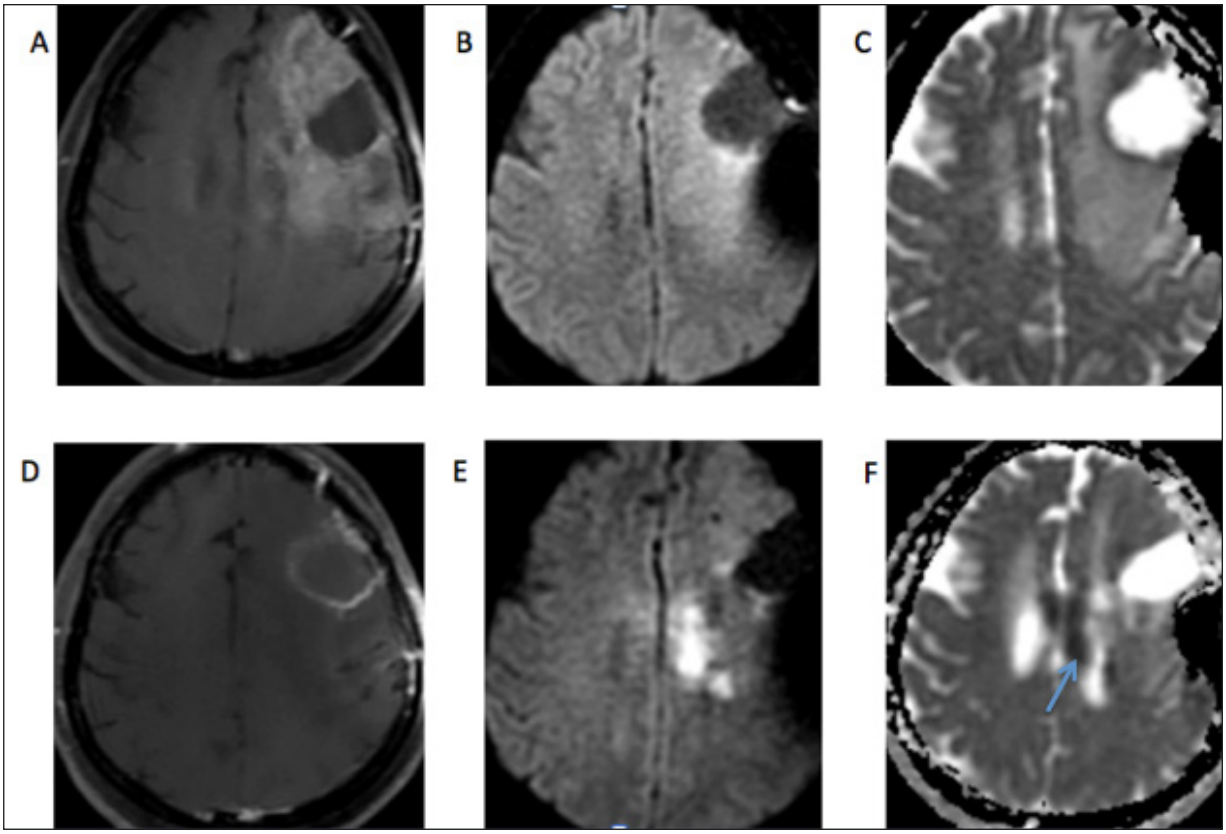

Figure 5. Axial post-contrast T1-weighted (**A**), diffusion-weighted imaging (**B**), ADC (**C**) at pre-BEV scan and corresponding images at first post-BEV scan (**D-F**). Patient had lower ADC values (arrow) on first post-BEV MRI and expired seventeen months after the first post-BEV scan.

tained for up to 80 weeks[3]. In our study, diffusion restriction was also observed on the first month after the treatment initiation whereas in most of our patients we could detect the diffusion restriction as early as 3 months. For the maintenance of the restriction, our patient population also demonstrated a wide time range. In our study, the diffusion restriction was observed for up to 18 months but we also found that this restriction was maintained for up to 6 months after the cessation of the BEV treatment.

By analyzing the serial changes of these diffusion-restricted lesions, we also aimed to assess the pathology beneath the ADC changes. We tried to determine whether the presence of restricted-diffusion lesions was associated with tumor progression which would correlate with decreased survival or treatment-induced necrosis which would be expected to correlate with improved survival. Apart from measuring the ADC values that appear after the BEV treatment, we also investigated the location of the diffusion restriction. The most common location of these diffusion-restricted areas was along the ventricles. Similar studies[9] have stated the most common locations as corpus callosum and along the ventricles which was also compatible with our findings. In this study, while some of the diffusion restriction appeared at the tumor site, others were mostly located periventricular which was far from the tumor site. We observed that patients that developed diffusion restriction areas that appeared far from the tumor site after BEV treatment had longer survival periods with lower ADC values which are lower than expected from actively growing tumors. All tumors had eventually progressed but in the patient group with more than one year overall survival, the diffusion restriction site detected after BEV treatment was different from tumor progression site. Moreover, at the time of progression, the diffusion-restricted areas that were not seen at tumor progression site, had low rCBV and rCBF values in MR perfusion imaging. Therefore, we hypothesized that the pathology under the diffusion restriction in these cases would be BEV-induced coagulative necrosis and the degree

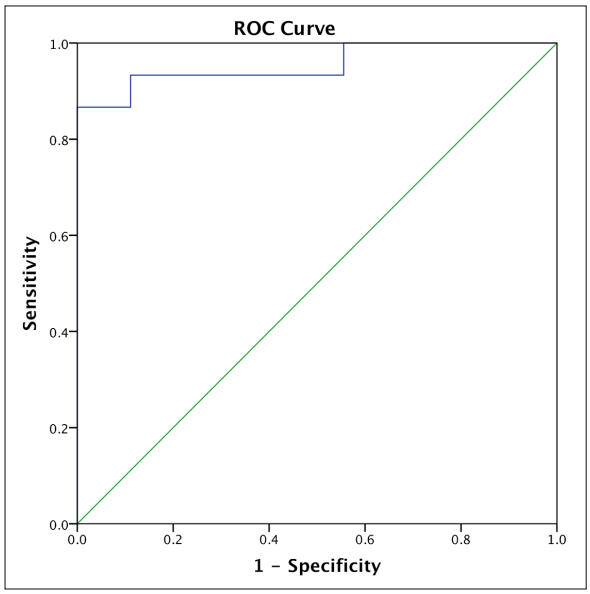

Figure 6. ROC analysis of ADC values for differentiating survival less than one year.

of diffusion restriction may serve as a useful tool to differentiate necrosis from tumor recurrence. This suggests that very low ADC values observed other than in the tumor site, that probably indicates treatment-induced necrosis at first post-BEV MRI scan, can predict longer survival periods. In addition, this situation can be interpreted as observing treatment-induced necrosis at first post treatment scan can be an important imaging marker showing effectiveness of BEV treatment and predicting survival.

Limitations

Our study has several limitations. First, it was a retrospective study and the study population is relatively small. In addition, we could not include follow-up ADC values in patients who died under bevacizumab treatment. Moreover, the frequency of MR follow-up imaging was not consistent among the patients. This lack of consistency led to less accurate tracking of changes in patients with less frequent imaging. Besides, we had no control over variables of therapy. All patients received adjuvant temozolomide, but the dosage varied depending on tumor response and patient tolerance of the drug. Our most important limitation would be that we could not provide histopathologic validation with autopsy and biopsy which was not possible because of the retrospective nature of the current study and because resection was not performed at recurrence. Instead, advanced imaging modalities and follow-up clinical and imaging findings were used to clarify whether these lesions represent treatment effect or tumor progression. Additional histopathological examinations from the site of diffusion restriction are necessary to definitively estimate the etiology of these lesions and more targeted biopsies coordinated with the imaging findings would be helpful for future investigations.

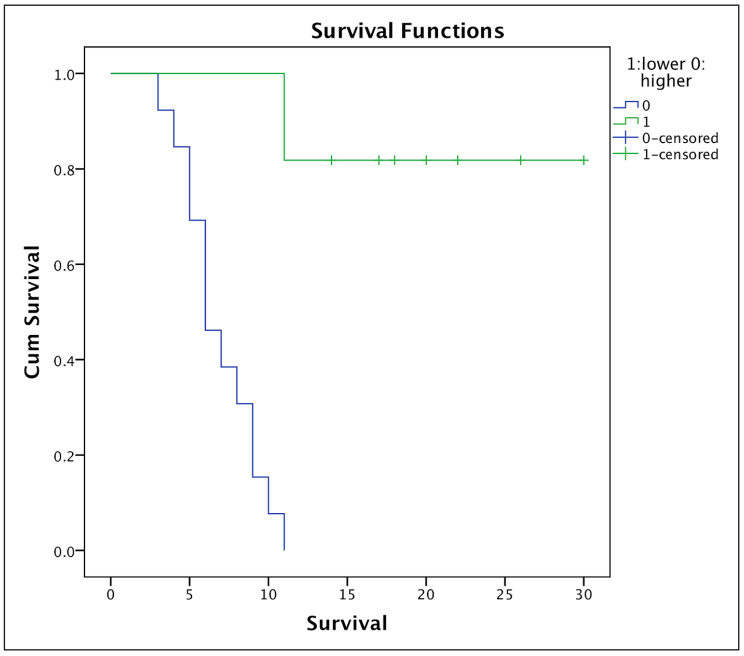

Figure 7. One-year survival of BEV therapy induced patients with diffusion restriction, when ADC threshold of 0.697×10^{-3} mm^2/s was implemented.

Conclusions

In patients with recurrent glial tumor treated with BEV, diffusion restriction can be observed after the initiation of the treatment. We determined that the ADC values obtained from these areas at first post-bevacizumab MRI scan correlate with progression free and overall survival with the worst survival seen in patients with higher ADC values which therefore can be considered as an imaging marker that can predict the prognosis. Additionally, analyzing the location of the diffusion restriction along with the ADC values might also contribute understanding the pathology that causes diffusion restriction, whether it is due to recurrence of tumor or treatment-induced necrosis. However, larger prospective trials are needed to confirm our findings.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

None.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Availability of Data and Materials

The datasets generated and analyzed during the current study are available from the corresponding author, (B.S.), upon reasonable request.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of SBU Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (2021-06/1220).

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Authors' Contributions

Burcu Savran had contributions to conception and design of the study, acquisition and analysis of data, drafting and writing the article, validation and final approval of the version of the article to be published. Mehmet Fatih Göç had contributions to acquisition and analysis of data, drafting the article and final approval of the version of the article to be published. Funda Ulu Öztürk had contributions to analysis and interpretation of data, drafting the article and final approval of the version of the article to be published. Ayşe Ocak Duran had contributions to acquisition of data, drafting the article, validation, and final approval of the version of the article to be published. Özkan Ünal had contributions to conception and design of the study, acquisition of data, making critical revisions related to relevant intellectual content of the manuscript, supervision, validation, and final approval of the version of the article to be published. All authors have read and agreed to the published version of the manuscript.

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