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Correlation of ADC Map with the Ki-67 Index in Glial Tumor Prognosis in Patients of Stereotaxic Ward

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ABSTRACT

Background and Purpose: There has been no report in which preoperative evaluation of ADC for prediction of post therapeutic outcome was presented. The aim of our study was to retrospectively evaluation the use of the apparent diffusion coefficient (ADC) for the prediction of malignancy and the outcome of malignant astrocytic tumors.
Methods: We reviewed MRI of 26 male and 14 female patients with a pathologic diagnosis of a malignant astrocytic tumor.
Results: There was a relatively significant correlation between Ki-67 LI and minimum ADC was noted for the asterocitoma group (r=−0.701, P<0.001) or the oligodendroglioma group (r=−0.634, P =0.027) and more significantly in oligoastrocitoma group (r=−1.000) separately. There was a significant negative correlation between these parameters for the malignant glial and oligodenroglial tumors as a whole (r=−0.634, P =0.027).
Conclusion: The ADC analysis could be considered as one of the clinically accessible techniques used for prediction of outcome of malignant astrocytic tumors, and it might be useful for planning primary treatment modality in patients with these malignant tumors.

Keywords: Astrocytic Tumors; Apparent Diffusion Coefficient; Diffusion Weighted; Labeling Index

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INTRODUCTION

Astrocytic tumors are the most common primary brain tumors and responsible for more than 70% of all gliomas [1]. The overall outcome of malignant astrocytic tumors, especially glioblastomas (GBMs), is still poor in even with aggressive treatments [1,2]. However, the outcome of these tumors differs from patient to patient. Some patients have relatively good outcome, and others have a very poor outcome, even with the same histopathologic diagnosis and similar treatments.

More precise pathologic study of tumor malignancy that might tightly associate with the patient's prognosis would affect treatment planning. Ki-67 labeling index (LI) is one of such optional immunohistochemical study for the assessment of tumor proliferation [3–6]. This index has become an essential component of histologic evaluation and postsurgical determination of grade for brain tumors, as a higher rate of Ki-67–positive cells related to a greater malignancy of brain neoplasms. This method, however, can be used in tumor specimens of surgical intervention. The method that make possible preoperative evaluation of tumor malignancy to make a more effective therapeutic modality possible for improvement in the outcome has long been awaited.

Introduction of diffusion-weighted (DW) magnetic resonance (MR) imaging has enabled us to reach additional information obtained from microscopic movement of the water proton, which is not available by using conventional MR imaging. DW imaging has been used for diagnosis of tumor grades or differentiation of tumors, as well as

for diagnosis of ischemic stroke [7–14]. Several researchers found a negative relationship between the apparent diffusion coefficient (ADC) calculated from DW images and tumor cellularity [7,8,11,14,15]. Some studies involving the determining of grades to gliomas by using ADC revealed the application of ADC for such process [9,14], but others did not [12]. To our knowledge, there has been no report in which preoperative evaluation of ADC for prediction of post therapeutic outcome was presented. Thus, the aim of our study was to retrospectively evaluation the use of the ADC for the prediction of malignancy and the outcome of malignant astrocytic tumors.

MATERIALS AND METHODS

We reviewed the MR imaging finding from Shohada Hospital. We selected consecutive patients with a pathologic diagnosis of a malignant astrocytic tumor who underwent preoperative MR imaging studies, including isotropic DW imaging, between January 2013 and April 2016. We excluded patients who had undergone major therapeutic strategies, such as surgery or radiation therapy and chemotherapy, before initial MR imaging with DW imaging. Frothy patients met the criteria, and the group comprised 26 male and 14 female patients who were 16–77 years in age (mean, 43 years).

The ethics committee of Shahid Beheshti University, Tehran, Iran, approved this retrospective study and did not need patient informed consent. Medical records, pathologic reports, surgical notes, and results of all MR imaging findings for all the patients were available.

Pathologic Evaluation and Surgery

The pathologic diagnosis included 26 astrocytoma and 12 oligodendroglioma and 2 oligoasterocitoma. The diagnosis was determined with specimens obtained in biopsy, based on the World Health Organization criteria, by a neuropathologist with 10 years of experience. In addition to the conventional histopathological assessment, the Ki-67 LI was retrospectively determined in all patients. In this process, fields with the highest number of Ki-67–labeled cells were primarily selected through a generalized survey, and then a percentage of positively labeled cells was determined by measuring more than 1000 tumor nuclei at ×400 magnification.

Stereotactic biopsy was undertaken in 38 patients, and these patients included one with GBM and six with AAs. All of the procedures were performed by one neurosurgeon with 40 years of experience. Biopsy included nonenhanced components of lesions and enhanced lesions.

MR Imaging and Data Processing

The patients were imaged by using a 1.5-T MR imaging system (Signa Horizon LX CV/i; GE Medical Systems, Milwaukee, Wis) and a conventional quadrature head coil. The contrast agent was gadodiamide injection. Nonenhanced and contrast-enhanced T1-weighted MR images, T2-weighted MR images, and DW images were obtained during the same imaging session without repositioning each patient's head.

ADC maps were calculated from isotropic DW images and images obtained with a *b* value of 0 sec/mm^2 by using standard software with a different workstation The minimum ADC value of each tumor was determined by placing ROI by using the same workstation as was used to generate ADC maps in the following procedures. We at first selected all continuous portions that included tumor. Several round- or oval-shaped regions of interest (area, approximately 0.3 cm^2, 10 pixels) were carefully insert each selected part of the ADC map to include the site with the lowest ADC value determined with visual inspection, preferably with avoidance of cystic, necrotic, or hemorrhagic portions of the tumor with reference to conventional MR images. Finally, a value of a region of interest with the lowest ADC value was chosen from these regions of interest as a minimum ADC value of the tumor.

Statistical Analysis

The correlation between minimum ADC and Ki-67 LI was analyzed by using correlational analysis (Pearson product moment correlation). In comparing every parameter between three groups equality of variances was evaluated by using the *F* test to select statistical tests.

RESULTS

There was a relatively significant correlation between Ki-67 LI and minimum ADC was noted for the asterocitoma group ($r=-0.701$, $P<0.001$) or the oligodendroglioma group ($r=-0.634$, $P=0.027$) and more significantly in oligoastrocitoma group ($r=-1.000$) separately (Table 1). There was a significant negative correlation between these parameters for the malignant glial and oligodenroglial tumors as a whole ($r=-0.634$, $P=0.027$). In regard to patient age, pretreatment performance status, minimum ADC value, and Ki-67 LI, compared between low grade and high grade groups in glial tumors. Minimum ADC value for the high grade group was significantly lower than that for the low grade group (Figure 1-5).

Table 1. Correlation between Ki-67 LI and minimum ADC for different tumors.

Correlations		
Tumor	**Ki67**	**ADC**
Oligo		
Ki67		
Pearson Correlation	1	-.634*
Sig. (2-tailed)		.027
N	12	12
ADC		
Pearson Correlation	-.634*	1
Sig. (2-tailed)	.027	
N	12	12
Astro		
Ki67		
Pearson Correlation	1	-.701**
Sig. (2-tailed)		.000
N	26	26
ADC		
Pearson Correlation	-.701**	1
Sig. (2-tailed)	.000	
N	26	26
oligo-Astro		
Ki67		
Pearson Correlation	1	-1.000**
Sig. (2-tailed)		.
N	2	2
ADC		
Pearson Correlation	-1.000**	1
Sig. (2-tailed)	.	
N	2	2

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

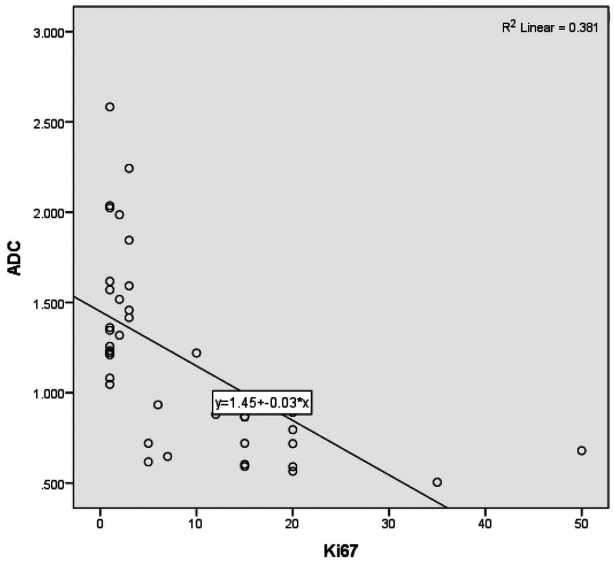

Figure 1. Graph shows ADC value in correlation with ki67 in determining glial tumor malignancy grade, there was a significant negative correlation between these parameters for the malignant glial and oligodenroglial tumors as a whole ($r = -0.634$, $P = 0.027$).

DISCUSSION

We found a significant inverse correlation between minimum ADC and Ki-67 LI for the malignant astrocytic and oligodendroglial tumors in general. Few reports have been presented in which a direct comparison of ADC values with the Ki-67 LI was performed. Calvar et al reported a marked inverse relationship between ADC values and Ki-67 LI in their analysis of 37 brain tumors with different pathologic findings [17]. Findings in many studies, suggest that ADC values are negatively correlated and the choline signal at proton MR spectroscopy is

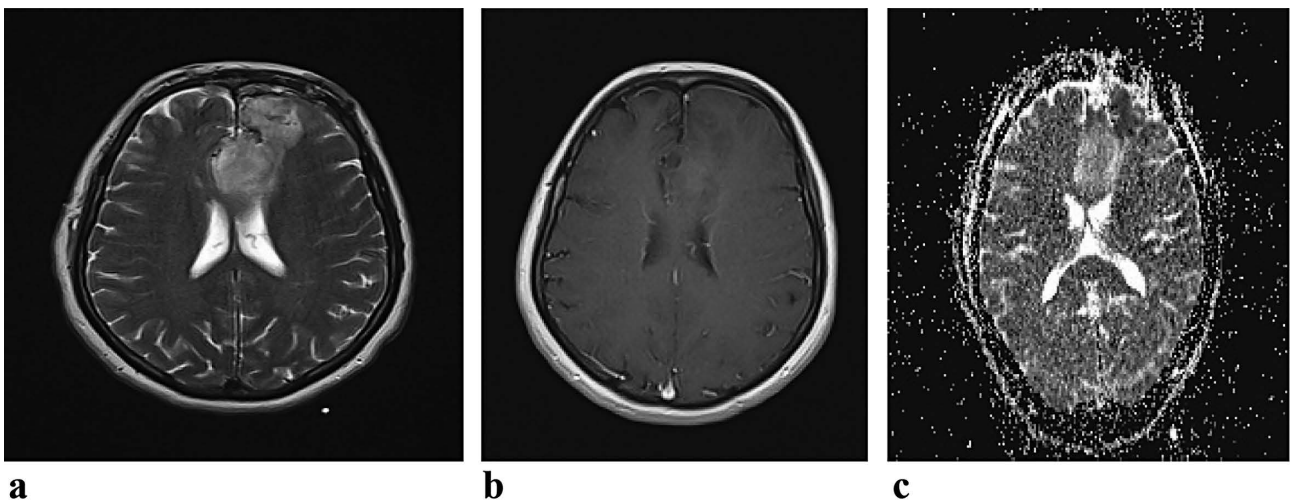

Figure 2. Oligodandroglioma grade II in 46-year-old woman. Transverse (a) preoperative T2-weighted MR image (3600/96), (b) contrast-enhanced T1-weighted MR image (440/14), and (c) ADC map show irregularly shaped enhancing tumor (arrows in a) with perifocal edema in left mediofrontal lobe. Minimum ADC value was 1.257×10^{-3} mm^2 · sec^{-1}.

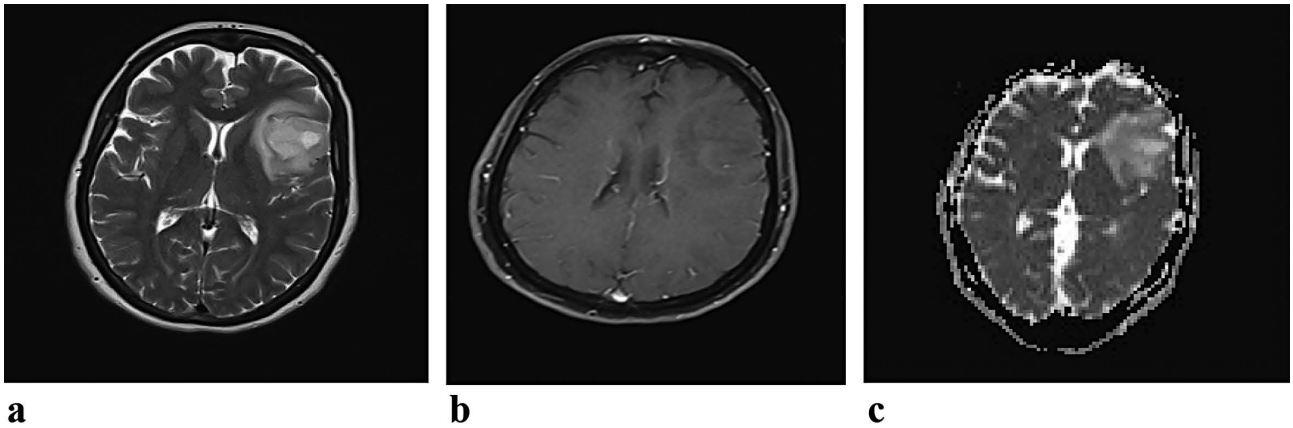

Figure 3. Asterocytoma grade II in 43-year-old woman. Transverse (a) preoperative T2-weighted MR image (3600/96), (b) contrast-enhanced T1-weighted MR image (440/14), and (c) ADC map show ill-defined tumor (arrows in a) in left insulo-opercular region. Irregular non enhancing area is noted in center of tumor (arrow in b). Minimum ADC value was 2.036×10^{-3} mm^2 · sec^{-1}.

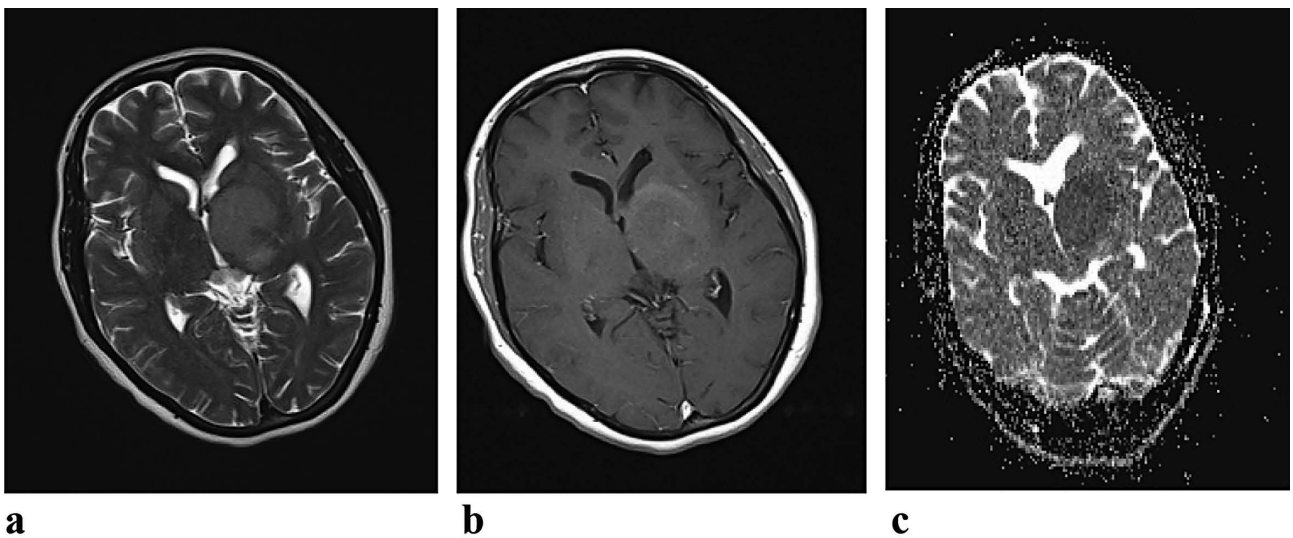

Figure 4. Anaplastic astrocytoma in 34-year-old woman. Transverse (a) preoperative T2-weighted MR image (b) contrast-enhanced T1-weighted MR image and (c) ADC map show well circumscribed shaped enhancing tumor (arrows in a) with minimal edema in left basal ganglia. Minimum ADC value was 0.592×10^{-3} mm^2 · sec^{-1}.

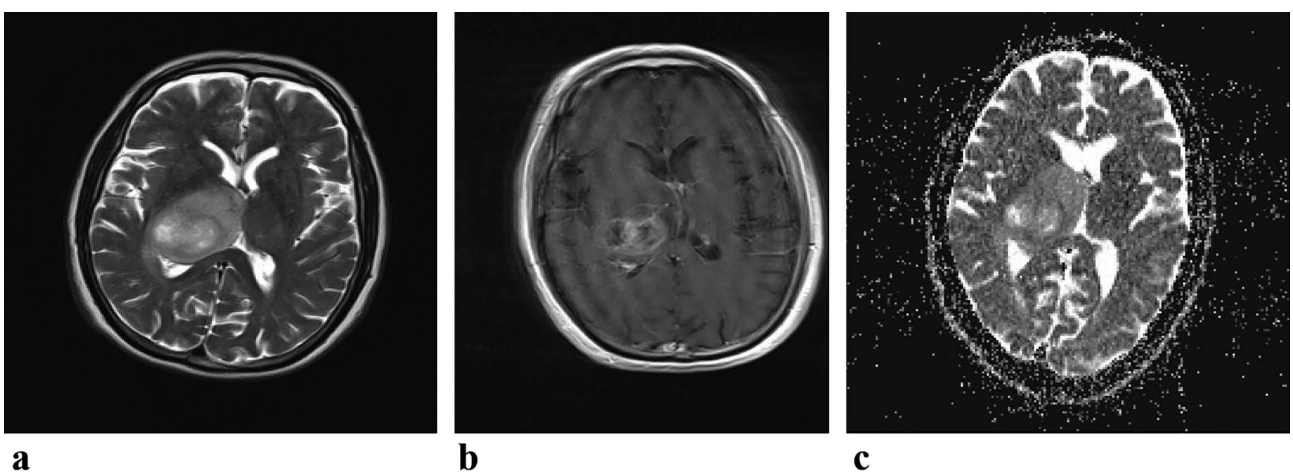

Figure 5. GBM in 43-year-old man. Transverse (a) preoperative T2-weighted MR image (3600/96), (b) contrast-enhanced T1-weighted MR image (440/14), and (c) ADC map show welldefined tumor (arrows in a) in right thalamus region. Irregular enhancing area is noted in center of tumor (in b). Minimum ADC value was0.891×10^{-3} mm^2 · sec^{-1}.

directly related to tumor cell density in various kinds of brain tumors [7,8,11,14,15]. Findings in several reports show that there is an negative relation between ADC values and choline signal in gliomas at MR spectroscopy [7,8].

In a MR spectroscopic study of astrocytomas, Tamiya et al found that the choline-creatine ratio related positively to Ki-67 LI and that the *N*-acetylaspartate–choline ratio correlated negetively with Ki-67 LI, and they offer that the choline signal at MR spectroscopy should suggestive gorcellular proliferation [18]. Considering all these results together, it is understandable that the ADC values related to the Ki-67 LI. It is likely that tumors with high proliferation index (high Ki-67 LI) should have capacity of rapid growth, yielding high cellularity. Kiss et al histopathologically evaluated cell density and Ki-67 LI in 54 astrocytic tumors and found a meaningful relationship between them [3].

Because our research was retrospective, the locations for measuring the minimum ADC did not precisely correspond to those for the Ki-67 LI. This might be one reason why the significant relationship was not detected for AA and GBM groups separately, because these gliomas are often very heterogeneous. The following discussion, however, may justify the meaning of the significant relationship between these parameters in all cases. The Ki-67 LI, which was obtained from the fields packed most closely with labeled cells, should have reflected the value from one of the portions with the highest cell density in the specimen. Similarly, the minimum ADC value should be suggestive for the value of the site with the highest cellularity of each tumor.

There was a significant difference in the mean minimum ADC values between the low grade glial tumors and high grade (III, IV) groups (Figure 2,3). In many researches regarding the assignment of grades to gliomas, researchers found a marked difference in tumor ADC values between low-grade (World Health Organization grades I and II) and high-grade (World Health Organization grades III and IV) gliomas and/or metastases [9,10,14]. As far as we know, however, no researchers suggested a significant difference in ADC between high-grade gliomas, that is Anaplastic Astrocytoma (AA) (grade III) and GBM (grade IV) (Figure 4,5). Most researchers assessed diffusional features in different pathologic types of tumors altogether rather than in a single type of tumor. Because the tumor cell density would be inherently different in each pathologic type, the same World Health Organization grade of different kinds of tumors may differ in based on their cell density.

The mean minimum ADC value of the stable group was meaningfully higher than that of the progressive group. A meaningful difference in Ki-67 LI was also found between these two groups. Several researchers have showed the prognostic importance of Ki-67 LI in astrocytic tumors [3,5,6]. Kiss et al observed that there was a marked difference in survival periods between the patients with a tumor that revealed a low level of Ki-67 LI and low cell density and those with a tumor that showed a high level of Ki-67 LI and high cell density [3]. Torp found that Ki-67 LI increased obviously with increasing malignancy grade of astrocytomas and that tumors with the higher Ki-67 LI had significantly poorer outcome than those with lower indexes [5]. Neder et al also reported a close relationship between MIB-1 LI (equivalent to Ki-67 LI) and survival of patients with astrocytomas [6].

Such an index is measurable only after harvesting samples of tumor specimens. We could not find any published reports that exhibited the usefulness of preoperative evaluation of tumor ADC for prediction of posttherapeutic outcome. Oh et al investigated the relationship between ADC values and survival time in patients with GBM [19]. They compared ADC values after surgery but before radiation therapy with patient survival times, and they suggested that there was a significantly shorter median survival time in patients with low ADC compared with that in patients with high ADC within the residual site of T2 elongation.

In this study, the outcome of each tumor after primary treatments (surgery or radiation therapy and chemotherapy) could be well predicted by using preoperative calculation of the minimum ADC of the tumor. The threshold values of 0.90×10^{-3} $mm^2 \cdot sec^{-1}$) in minimum ADC provided the best combination of sensitivity and specificity for prediction of outcome. Actually, when we compared the prognosis between the three groups categorized by using this threshold, the group with the higher minimum ADC had a significantly better outcome. When we considered the result that showed a deramatic correlation between minimum ADC and Ki-67 LI, it was not surprising that tumoral minimum ADC values should have preoperative prognostic importance in patients with a malignant astrocytoma.

Stereotactic biopsy often is done to make a diagnosis in patients with intracranial lesions. As gliomas are generally heterogeneous and can have different histologic grades in a single tumor, the wrong choice of biopsy portion may result in underestimation of a tumor grade, and underestimation may confound determination of the best treatment modality. In such a situation, calculation

of minimum ADC may aid in the selection of the optimal portion for the biopsy, because minimum ADC should exhibit a site with the highest tumor cell density, or the most highly proliferative site of the tumor.

Several tumor-specific factors such as necrosis and neovascularity may affect prognosis [2]. Results of many studies have revealed the usefulness of MR spectroscopy and MR perfusion imaging, which can show necrosis or neovascularity, in addition to ADC measurements for the prediction of grade or malignancy of brain tumors [18,20]. Some researchers suggested the advantages of a combination of these methods [10,21]. Among the different noninvasive techniques, however, DW imaging should be available in many hospitals and is the easiest to use and the least time consuming of them. The post processing of the data also is simple, and variation in the analyzed results should be minimum.

One of the limitations of this study was that there was no accordance of the areas for the minimum ADC measurement with those for the Ki-67 LI, which was already explained previously. A second limitation was that we used only the minimum ADC values of tumors for evaluation of the outcome. A patient's outcome is believed to depend on the most malignant portion within a heterogeneous tumor, and it is on the basis of this portion that the assignment of a histologic tumor grade generally is determined. As we have shown before, tumoral ADC should relate well to the cell density and Ki-67 LI. Thus, it may be reasonable to think the location with minimum ADC value should represent one of the most malignant parts of the tumor. When the postoperative outcome is considered, however, aggressiveness of the peripheral sites of a tumor might be more important than the central sites because the peripheral parts, where tumor recurrence usually happens, tend to remain after surgery. Considering this, the minimum ADC values of the peripheral site might correlate better with the outcome

In conclusion, minimum ADC values of the tumor were well related to the Ki-67 LI and were correlated with tumoral outcome. We believe that ADC analysis should be one of the clinically accessible techniques used for prediction of outcome of malignant astrocytic tumors, and it might be useful for planning primary treatment modality in patients with these malignant tumors.

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