doi: 10.17116/engneiro20157964-12

# A Correlation Between Diffusion Kurtosis Imaging and the Proliferative Activity of Brain Glioma

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The **aim** of the study was to assess the capabilities of diffusion kurtosis imaging (DKI) in diagnosis of the glioma proliferative activity and to evaluate a relationship between the glioma proliferative activity index and diffusion parameters of the contralateral normal appearing white matter (CNAWM). **Material and methods.** The study included 47 patients with newly diagnosed brain gliomas (23 low grade, 13 grade III, and 11 grade IV gliomas). We determined a relationship between absolute and normalized parameters of the diffusion tensor (mean (MD), axial (AD), and radial (RD) diffusivities; fractional (FA) and relative (RA) anisotropies) and diffusion kurtosis (mean (MK), axial (AK), and radial (RK) kurtosis; kurtosis anisotropy (KA)) and the proliferative activity index in the most malignant glioma parts ($p<0.05$). We also established a relationship between the tensor and kurtosis parameters of CNAWM and the glioma proliferative activity index ($p<0.05$). **Results.** The correlation between all the absolute and normalized diffusion parameters and the glioma proliferative activity index, except absolute and normalized FA and RA values, was found to be statistically significant ($p<0.05$). Kurtosis (MK, AK, and RK) and anisotropy (KA, FA, RA) values increased, and diffusivity (MD, AD, RD) values decreased as the glioma proliferative activity index increased. A strong correlation between the proliferative activity index and absolute RK ($r=0.71$; $p=0.000001$) and normalized values of MK ($r=0.8$; $p=0.000001$), AK ($r=0.71$; $p=0.000001$), RK ($r=0.81$; $p=0.000001$), and RD ($r=-0.71$; $p=0.000001$) was found. A weak, but statistically significant correlation between the glioma proliferative activity index and diffusion values RK ($r=-0.36$; $p=0.014$), KA ($r=-0.39$; $p=0.007$), RD ($r=0.35$; $p=0.017$), FA ($r=-0.42$; $p=0.003$), and RA ($r=-0.41$; $p=0.004$) of CNAWM was found. **Conclusion.** DKI has good capabilities to detect immunohistochemical changes in gliomas. DKI demonstrated a high sensitivity in detection of microstructural changes in the contralateral normal appearing white matter in patients with brain gliomas.

***Keywords:*** *diffusion tensor, diffusion kurtosis, glioma, malignant, proliferative activity.*

**Abbreviations**

AD — axial diffusion
AK — axial kurtosis
HGG — high-grade glioma
LGG — low-grade glioma
DKI — diffusion kurtosis imaging
DTI — diffusion tensor imaging
ZOI — zone of interest
KA — kurtosis anisotropy
CNAWM — contralateral normal appearing white matter
RA — relative anisotropy
RD — radial diffusion
RK — radial kurtosis
MD — mean diffusion
MK — mean kurtosis
FA — fractional anisotropy

Proliferative activity of gliomas and their degree of malignancy, localization, size and spread of the tumor, completeness of the tumor's surgical removal, as well as a patient's age and neurological status are very important for the disease prognosis and survival [1]. Several methods have been developed to date to assess proliferative activity of the tumors [2, 3] with Ki-67/MIB-1 labelling index (Ki-67/MIB-1 LI) being the most reliable and the most common way of assessing mitotic activity [4].

A review [5] of 16 works, which included 915 patients, demonstrates statistically significant increase in Ki67/MIB-1 LI with increasing grade of brain astrocytomas. For astrocytomas, Ki-67/MIB-1 LI values above 10% are considered to be indicative of high malignancy potential [5]. Statistically significant correlation has also been demonstrated for Ki-67/MIB-1 LI and prognosis, survival and tumor recurrence [5—8]. Furthermore, Ki-67/MIB-1 LI is believed to be a more important marker for gliomas prognosis than their histologically defined tumor grade (WHO grade) [8, 9].

The data of standard MRI with intravenous contrast display good correlation with Ki-67/MIB-1 LI values: gliomas that accumulate the contrast medium are characterized by average Ki-67/MIB-1 LI values up to 8.1%, while the tumors without contrast enhancement typically have values of about 2.0% ($p=0.0007$) [10]. However, determination of Ki-67/

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MIB-1 LI value in a tumor using the standard MRI technique is a rather challenging task.

A number of published papers [7, 11—19] is devoted to a correlation between diffusion tensor MRI (DTI) parameters, namely mean diffusion and fractional anisotropy, and Ki-67/MIB-1 LI.

Diffusion kurtosis imaging (DKI) is a novel neuroimaging technique, which has been gaining traction in the recent years and demonstrates higher sensitivity in characterization of the brain tissues microstructure under normal and pathological conditions. DKI can be used to quantify a number of parameters:

• mean, axial and radial kurtoses (MK, AK and RK), which describe resistance to molecular transport (SK, mean resistance, AK, resistance along the axons, RK, resistance in the plane perpendicular to the axons, respectively);

• kurtosis anisotropy (KA), which describes the homogeneity of resistance to molecular transport in different directions;

• mean, axial and radial diffusion (MD, AD and RD), which describe flow rates of molecules (MD, average flow rate, AD, flow rate along the axons, RD, flow rate in the plane perpendicular to the axons, respectively);

• fractional and relative anisotropy (FA and RA), which describe the uniformity (isotropy) of the molecular flow rate in different directions.

There are no papers in Russian and foreign literature on the use of DKI in the diagnosis of the gliomas proliferative activity. Our paper is the first publication describing an attempt to correlate Ki-67/MIB-1 LI proliferative activity index with gliomas DKI parameters; we are also the first to study a relationship between diffusion kurtosis parameters of the contralateral normal appearing white matter (CNAWM) and gliomas Ki-67/MIB-1 LI values. Our work is also the first one to use a number of additional diffusion tensor parameters (axial and radial diffusion, relative anisotropy) in the study of gliomas Ki-67/MIB-1 LI values; the authors of the previously published papers mainly used average diffusion and fractional anisotropy.

## Material and Methods

The study was approved by the ethics committee of the Burdenko Neurosurgical Institute. All patients signed a written informed consent form to participate in the study. The study included 47 patients with supratentorial gliomas of the brain. These patients were diagnosed and treated at the Burdenko Neurosurgical Institute. All gliomas were newly diagnosed, with no prior surgery, radiation or chemotherapy. Patients with history of other cancers were excluded from the study. All patients underwent surgical removal of the tumor or stereotactic biopsy within 1—2 weeks after the DKI. For all patients, the morphological diagnosis and Ki-67/MIB-1 LI values of the tumors were confirmed by histopathological and immunohistochemical studies.

The study included 24 patients with high-grade gliomas (HGG) (11 grade IV gliomas and 13 grade III gliomas) and 23 patients with low-grade gliomas (LGG) (20 grade II gliomas and 3 grade I gliomas). Grade IV gliomas included 10 glioblastomas and 1 gliosarcoma. Grade III gliomas included 12 anaplastic astrocytomas and 1 anaplastic oligoastrocytoma. Grade II gliomas included 18 diffuse astrocytomas and 2 oligoastrocytomas. Grade I gliomas included 2 gangliocytomas and 1 subependimal giant cell astrocytoma. The group of patients included in our study consisted of 29 men and 18 women; the average age of the HGG patients was 43.8±14.7 years, the average age of the LGG patients was 37.7±9.6 years.

DKI was performed on MRI scanner with 3.0 Tesla magnetic induction, using echoplanar spin echo (SE-EPI) pulse sequence, three values of diffusion factor b (0, 1000 and 2500 s/mm$^2$) and 60 directions of diffusion gradients for each non-zero b-factor. The following the pulse sequence parameters were chosen for the study: TR=10,000 ms, TE=103.4 ms, FOV=240×240 mm, 80×80 image matrix with subsequent interpolation up to 256×256, 3 mm slice thickness, 0 mm distance between slices, NEX=1, axial scanning plane. The duration of DKI scan was 22 minutes. Additional anatomical images were obtained in the axial plane, consisting of the T2 WI scans (TR=4,300 ms, TE=85 ms, turbo factor of 21, FOV=240×240 mm, 512×512 image matrix, 3 mm slice thickness, 0 mm distance between slices, NEX=2) and T2-FLAIR WI scans (TR=9,500 ms, TE=120 ms, TI=2,250 ms, FOV=240×240 mm, 352×325 image matrix, 5 mm slice thickness, 0 mm distance between slices, NEX=1) registered before intravenous administration of the contrast and T1 WI scans (TR=875 ms, TE=85 ms, FOV=240×240 mm, 384×384 image matrix, 3 mm thickness of slices, 0 mm distance between slices, NEX=2), registered before and after intravenous administration of Gd-containing contrast (at a concentration of 0.1 mmol Gd per 1 kg of a patient's weight). DKI was performed before the contrast enhancement.

Post-processing of the resulting DKI data set was performed in a number of software packages: MATLAB (MathWorks, USA, http://www.mathworks.com/), FSL (FMRIB Software Library v5.0, Oxford, UK, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) [20—22], ExploreDTI (the Netherlands, http://www.exploredti.com/), ITK-Snap (www.itksnap.org) [23], Mango (http://www.nitrc.org/projects/mango). The following quantitative parameters of diffusion kurtosis and diffusion tensor were obtained after the processing: mean kurtosis (MK), axial kurtosis (AK), radial kurtosis (RK), kurtosis anisotropy (KA), mean diffusion (MD), axial diffusion (AD), radial diffusion (RD), fractional anisotropy (FA), relative anisotropy (RA).

The zones of interest (ZOIs) for measuring diffusion parameters in the solid part of the tumor **(Fig. 1)** and in the zone of the contralateral normal appearing white matter (CNAWM) (**Fig. 1c**) were selected manually at the maps of mean kurtosis using ITK-SNAP and anatomical MRI data (T1 WI scans before and after contrast enhancement, T2 WI and T2-FLAIR WI scans). The selected ZOIs were automatically transferred to the maps of all other diffusion parameters. Cystic and necrotic tumor components and peritumoral edema of the brain tissue were excluded from the ZOIs.

It is well known that with time most gliomas progress towards the state of higher malignancy and higher proliferative activity [24]. However, many glial tumors have heterogeneous structure, which can simultaneously contain areas with different degrees of malignancy and proliferative activity. In pathomorphology, the true degree of malignancy and proliferative activity of a tumor are defined as the highest values for a part of the tumor. Therefore, in our study the ZOIs included only parts of the tumor with the highest MK values **(Fig. 1)**, which, in our opinion, corresponded to the most malignant parts of the tumor, and, hence, those with the highest proliferative activity [25]. The ZOIs did not include tumor infiltration zones containing brain tissue, which could have

increased values for kurtosis and anisotropy and reduced those for diffusion **(Fig. 2)**.

Kurtosis and tensor parameters of the tissues and structures of the brain vary based on localization of the tumor, age and gender of the patient [26—30]. Since diffuse gliomas are characterized by diffuse infiltrative growth in the brain matter, their diffusion parameters may depend on diffusion properties of the brain tissues. In order to compensate for the aforementioned individual features, we have calculated normalized tumor diffusion parameters based on the corresponding parameters of the CNAWM, using the following formula: normalized MK=MKtumor/MKCNAWM, and so on for each parameter (**Fig. 1c**).

The following goals have been achieved during the study.

1. Investigation of the correlation between gliomas Ki-67/MIB-1 LI values and their absolute and normalized diffusion parameters.
2. Investigation of the correlation between gliomas Ki-67/MIB-1 LI values and diffusion parameters of the CNAWM.
3. Investigation of the correlation between gliomas Ki-67/MIB-1 LI values and their degree of malignancy.
4. Investigation of the correlation between gliomas Ki-67/MIB-1 LI values and accumulation of the contrast.
5. Investigation of the correlation between gliomas degree of malignancy and accumulation of the contrast.

Spearman correlation coefficients were used in all cases, and the threshold of statistical significance was set at $p<0.05$. According to generally accepted mathematical standards, a correlation was considered to be very weak for $0<r\leqslant0.2$, weak for $0.2<r\leqslant0.5$, average for $0.5<r\leqslant0.7$, strong for $0.7<r\leqslant0.9$, and very strong for $0.9<r\leqslant1$.

## Results

The correlations between the gliomas proliferative activity index (Ki-67/MIB-1 LI) and their diffusion parameters are presented in **Table 1**. The correlation between the glioma proliferative activity index (Ki-67/MIB-1 LI) and all absolute and normalized diffusion parameters, except for absolute values of FA and RA, was found to be statistically significant and reliable ($p<0.05$). Kurtosis (MK, AK, and RK) and anisotropy (KA, FA, RA) values increased, and diffusivity (MD, AD, RD) values decreased with the increase in the glioma proliferative activity index. The proliferative activity index was strongly correlated with absolute RK ($r=0.71$; $p=0.000001$) and normalized MK ($r=0.8$; $p=0.000001$), AK ($r=0.71$; $p=0.000001$), RK ($r=0.81$; $p=0.000001$) and RD ($r=-0.71$; $p=0.000001$). Normalized values of RK and MK displayed the strongest correlation with gliomas Ki-67/MIB-1 LI values **(Fig. 3)**.

The correlations between the gliomas proliferative activity index (Ki-67/MIB-1 LI) and the CNAWM diffusion parameters are shown in **Table 2**. Statistically significant weak correlation was observed for RK ($r=-0.36$; $p=0.014$), KA ($r=-0.39$; $p=0.007$), RD ($r=0.35$; $p=0.017$), FA ($r=-0.42$; $p=0.003$), and RA ($r=-0.41$; $p=0.004$) values of the contralateral white matter of the brain.

The analysis performed in our study confirmed an opinion expressed by other authors that the standard MRI with intravenous contrast has only limited capabilities in diagnostics of gliomas degree of malignancy and proliferative activity. According to our data (**Table 3**), there is a weak positive correlation between gliomas Ki-67/MIB-1 LI values and contrast enhancement ($r=0.37$; $p=0.0148$) and an average positive correlation between gliomas histological grade and contrast enhancement ($r=0.5$; $p=0.0001$), whereas the correlation between gliomas Ki-67/MIB-1 LI values and degree of malignancy is very strong ($r=0.91$; $p=0.0001$).

## Discussion

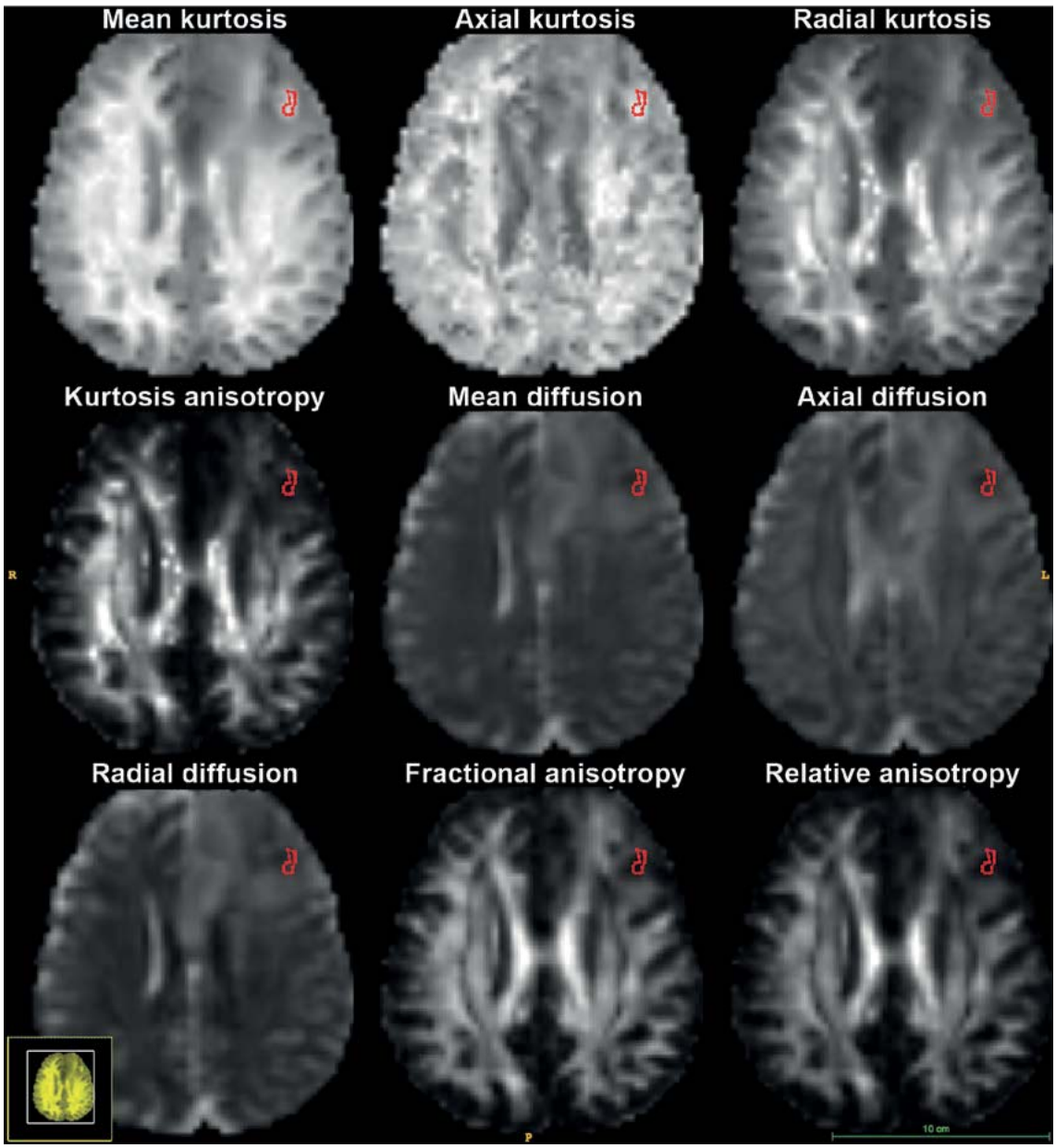
Nowadays, diffusion-weighted imaging and DTI are widely used in preoperative diagnosis of glial neoplasms [7, 11—17, 28, 31—45]. The technique allows the characterization of isotropic and anisotropic diffusion, based on the assumption that molecular diffusion in the brain tissue has Gaussian distribution. However, the presence of a large number of microstructural units in the brain tissues (cells, cell membranes and organelles, multidirectional nerve processes, extracellular and intracellular liquids, membrane ion pump, etc.) complicates and hinders molecular diffusion, which is, in fact, non-Gaussian in nature. DKI has been successfully used to describe the non-Gaussian diffusion, allowing simultaneous assessment of both Gaussian and non-Gaussian components of molecular diffusion [46, 47]. DKI provides neuroradiologists with a whole arsenal of quantitative parameters that characterizes the microstructure of the brain: diffusion tensor parameters (MD, AD, RD, FA,RA), which can also be obtained with DTI, and diffusion kurtosis parameters (MK, AK, RK, KA) [30, 47].

A number of papers dedicated to the study of correlations between DTI parameters, namely MD and FA, and Ki-67/MIB-1 LI values have been published [7, 11—19]. A statistically significant negative correlation have been established between MD and Ki-67/MIB-1 LI [11, 13—15, 19], and a statistically significant positive one between FA and Ki-67/MIB-1 LI of gliomas [11, 13—16]. Other studies had revealed a statistically significant negative correlation between the minimal MD and Ki-67/MIB-1 LI values of gliomas [12, 18]. These works do not contradict our results. Yet, the literature data on correlations between the glial tumors proliferative activity index and DTI parameters are contradictory. Some authors [17] have come to the opposite conclusion, arguing that FA is negatively correlated and MD is positively correlated with gliomas Ki-67/MIB-1 LI values. Another study [7] failed to found statistically significant correlation between DTI parameters and Ki-67/MIB-1 LI values for glioblastomas.

A particular feature of our work was the investigation of a correlation between the proliferative activity index and diffusion parameters in the most malignant parts of glial tumors. Diffusion parameters were measured only in the solid parts of the tumors with maximum values of MK [25], and not in the entire volume of gliomas. Necrosis and cystic components of gliomas, peritumoral edema, and parts of the tumor containing the remnants of the brain tissue were excluded from the zones of measurement. Necrosis and cystic components of gliomas have low

values of kurtosis (MK, AK, RK) and anisotropy (KA, FA, RA), and high values of diffusion (MD, AD, RD) since their molecular diffusion is close to isotropic Gaussian in nature. The values of kurtosis, diffusion and anisotropy in peritumoral edema of the brain tissue and tumor areas, containing the residual white matter, differ from those in the central part of gliomas due to the presence of the nerve fibers residues [14, 25, 48].

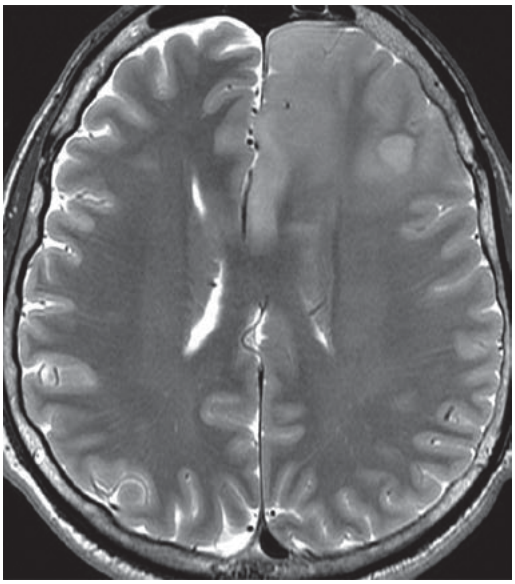
**Table 1** shows that all absolute and normalized diffusion parameters, except for absolute RA and FA, are statistically significantly correlated with Ki-67/MIB-1 LI. Higher Ki-67/MIB-1 LI values of gliomas imply more active division of the tumor cells and more rapid growth of the tumor, which lead to increased cell density in the tumor and reduction in the extracellular space. These factors complicate and limit the diffusion of water molecules in the tumor, and, in our opinion, are the



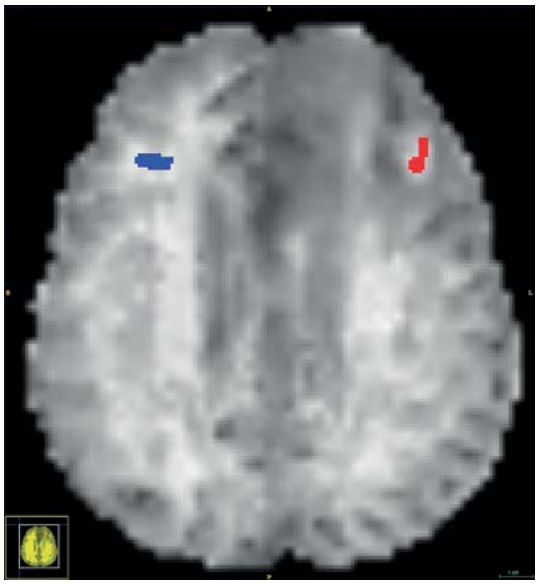

a

***Fig. 1.*** **Anaplastic astrocytoma of the left frontal lobe.**
a — diffusion parameters.

*Fig. 1 is continued on the next page*



b



c

***Fig. 1.* Anaplastic astrocytoma of the left frontal lobe.** *Continued.*

b — T2 WI; c — ZOIs around the tumor and the contralateral normal appearing white matter at the MK maps.
The zone of interest includes the parts of the tumor with maximum MK values, which corresponds to the maximum malignancy and proliferative activity.

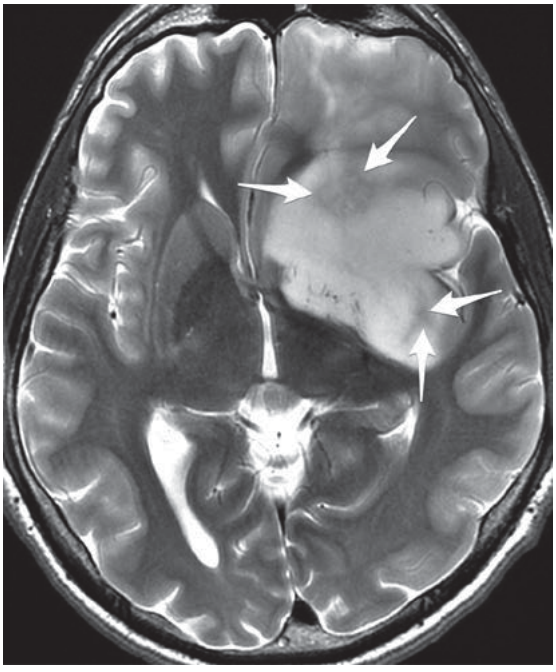


***Fig. 2.* Diffuse grade II astrocytoma, T2 WI.**

Arrows indicate the parts of the tumor containing residual brain tissue.

main reasons for the increase in kurtosis parameters (MK, AK, RK) and reduction in diffusion parameters (MD, AD, RD) with the increase in Ki-67/MIB-1 LI values. The reduction of intercellular space is also an important cause of statistically significant increase in anisotropy (absolute KA, normalized KA, FA, RA) with an increase in glial tumors Ki-67/MIB-1 LI values. Since glial tumors have neuroepithelial genesis and tend to exhibit diffuse and infiltrative growth into the brain tissue, the individual characteristics of patients (tumor localization, age, gender, etc.) may affect the diffusion parameters of the tumor. Therefore, we have performed normalization of gliomas diffusion parameters to the contralateral normal appearing white matter. Normalized MK ($r$=0.8; $p$=0.000001) and RK ($r$=0.81; $p$=0.000001) exhibited the strongest correlation with gliomas Ki-67/MIB-1 LI, which confirms the relevance of normalization. Diffusion kurtosis parameters showed better correlation with the proliferative activity index compared with diffusion tensor parameters. It can be attributed to the fact that kurtosis describes the non-Gaussian molecular diffusion typical for biological tissues.

There are some articles showing a statistically significant relationship between DKI parameters and gliomas degree of malignancy (WHO Grade), which report an increase in diffusion kurtosis parameters and anisotropy and decrease in diffusion tensor parameters with the increasing degree of malignancy [25, 49, 50]. Similar dynamics of diffusion parameters was observed in case of increase in the gliomas proliferative activity **(see Table 1)**, which corresponds to a very strong correlation between the proliferative activity and degree of malignancy **(see Table 3)**. The gliomas proliferative activity is one of the main factors determining their degree of malignancy (WHO Grade) and it affects the

***Table 1.*** **Correlation between Ki-67/MIB-1 LI values and diffusion parameters of the tumor**

| Indicator | Spearman correlation coefficient | *p*-value |
|---|---|---|
| Ki-67/MIB-1 LI & CK | 0.69 | 0.000001 |
| Ki-67/MIB-1 LI & AK | 0.68 | 0.000001 |
| Ki-67/MIB-1 LI & RK | 0.71 | 0.000001 |
| Ki-67/MIB-1 LI & KA | 0.36 | 0.012331 |
| Ki-67/MIB-1 LI & MD | –0.60 | 0.000008 |
| Ki-67/MIB-1 LI & AD | –0.61 | 0.000006 |
| Ki-67/MIB-1 LI & RD | –0.60 | 0.000009 |
| Ki-67/MIB-1 LI & FA | 0.21 | 0.158110 |
| Ki-67/MIB-1 LI & RA | 0.21 | 0.158110 |
| Ki-67/MIB-1 LI & norm CK | 0.80 | 0.000001 |
| Ki-67/MIB-1 LI & norm AK | 0.71 | 0.000001 |
| Ki-67/MIB-1 LI & norm RK | 0.81 | 0.000001 |
| Ki-67/MIB-1 LI & norm KA | 0.54 | 0.000102 |
| Ki-67/MIB-1 LI & norm MD | –0.69 | 0.000001 |
| Ki-67/MIB-1 LI & norm AD | –0.59 | 0.000011 |
| Ki-67/MIB-1 LI & norm RD | –0.71 | 0.000001 |
| Ki-67/MIB-1 LI & norm FA | 0.44 | 0.001987 |
| Ki-67/MIB-1 LI & norm RA | 0.44 | 0.002113 |

***Table 2.*** **Correlation between Ki-67/MIB-1 LI values and diffusion parameters of the CNAWM**

| Indicator | Spearman correlation coefficient | *p*-value |
|---|---|---|
| Ki-67/MIB-1 LI & CK | –0.17 | 0.242 |
| Ki-67/MIB-1 LI & AK | 0.15 | 0.302 |
| Ki-67/MIB-1 LI & RK | –0.36 | 0.014 |
| Ki-67/MIB-1 LI & KA | –0.39 | 0.007 |
| Ki-67/MIB-1 LI & MD | 0.22 | 0.125 |
| Ki-67/MIB-1 LI & AD | –0.17 | 0.245 |
| Ki-67/MIB-1 LI & RD | 0.35 | 0.017 |
| Ki-67/MIB-1 LI & FA | –0.42 | 0.003 |
| Ki-67/MIB-1 LI & RA | –0.41 | 0.004 |

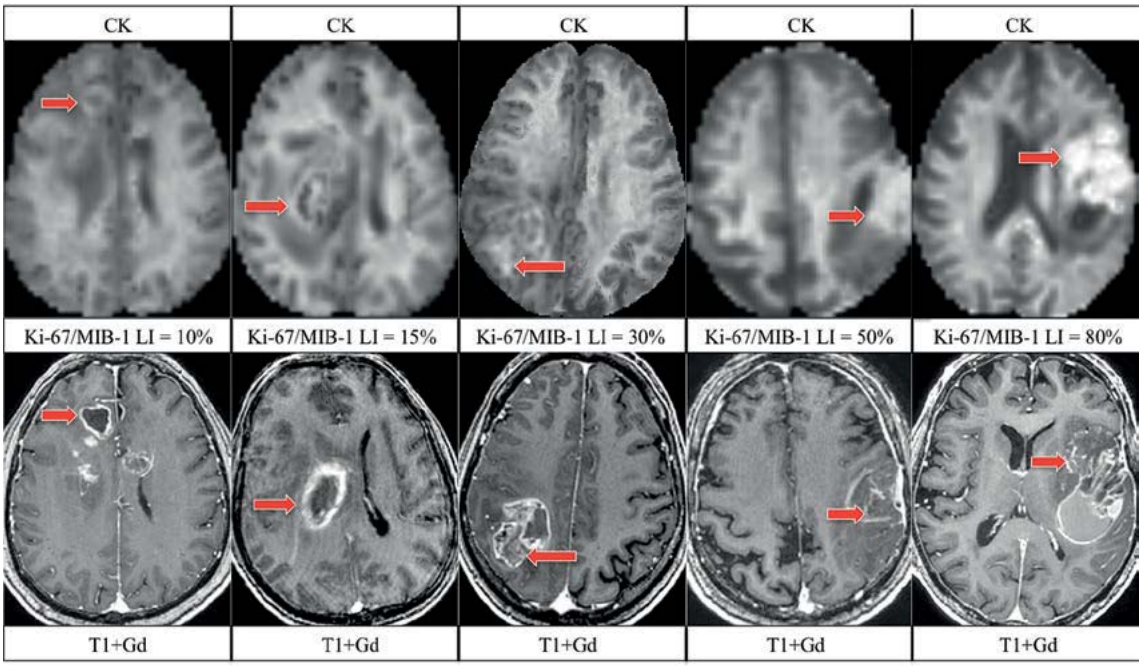



***Fig. 3.*** **Glioblastomas with different Ki-67/MIB-1 LI values.**

The increase in Ki-67/MIB-1 LI is accompanied by the marked increase in the tumors MK values, whereas all tumors have the same characteristics on T1 WI, nonuniform accumulation of contrast medium, a zone of necrosis, etc.

***Table 3.*** **Correlation between Ki-67/MIB-1 LI values, grade of the tumor (WHO Grade) and accumulation of the contrast**

| Indicator | Spearman correlation coefficient | *p*-value |
|---|---|---|
| Ki-67/MIB-1 LI & WHO Grade | 0.91 | 0.0001 |
| Ki-67/MIB-1 LI & accumulation of contrast agent | 0.37 | 0.0148 |
| WHO Grade & accumulation of contrast agent | 0.5 | 0.0001 |

***Table 4.*** **Age characteristics of the patients with high and low grade gliomas**

| Indicator | LGG | HGG | *p*-value |
|---|---|---|---|
| Number of patients | 23 | 24 | — |
| Patients age (*Mean*±*SD*), years | 37.7±9.6 | 43.8±14.7 | >0.1 |

values of the tumor diffusion parameters. Investigation of relationships between other factors that define gliomas degree of malignancy and DKI parameters is also of great scientific interest and could be a subject of further research.

**Table 2** shows that gliomas Ki-67/MIB-1 LI is statistically significantly correlated with some diffusion parameters of the contralateral normal appearing white matter. Several authors [51, 52] believe that diffuse glial tumors are systemic diseases of the central nervous system rather than local tumor processes. They have demonstrated the presence of the tumor cells in different brain structures, which were unaltered according to standard MRI, at a considerable distance from the glioma [52]. Statistically insignificant trend towards increase in AK and reduction in AD of the CNAWM with the increase in Ki-67/MIB-1 LI may reflect the increase in proliferation of glia or tumor cells and increase in the density of glial or tumor cells in the CNAWM as proliferative activity of the primary tumor intensifies. A significant reduction in RK ($r$=-0.36; $p$=0.014) and significant increase in RD ($r$=0.35; $p$=0.017) of the CNAWM with the increase in tumor Ki-67/MIB-1 LI may reflect the destruction of nerve fibers by tumor cells, which becomes more pronounced with increase in the glioma proliferative activity (since the average age of HGG and LGG patients is not significantly different (**Table 4**), the observed changes in RK and RD of the CNAWM cannot be attributed to development of atrophic changes in nerve fibers due to more advanced age of the patients). Statistically significant reduction in KA ($r$=-0.39; $p$=0.007), FA ($r$=-0.42; $p$=0.003) and RA ($r$=-0.41; $p$=0.004) values of the CNAWM with the increase in gliomas Ki -67/MIB-1 LI may be caused by both the destruction of the nerve fibers in the contralateral white matter and increased proliferation of tumor or glial cells.

One disadvantage of our study may be the fact that the ZOIs in gliomas were selected in the parts with the highest MK values, however it was not always known which exact portion of the tumor was subjected to pathomorphological and immunohistochemical examination. In future studies, higher number of patients will allow investigation of the relationship between DKI parameters and Ki-67/MIB-1 LI values within a group of patients with gliomas of one particular degree of malignancy (to exclude the influence of other factors, which constitute the degree of malignancy, on the diffusion parameters values, e.g. vascularization, nuclear atypia, number of mitoses, micronecrosis etc.) and with a specific histological subtype of gliomas (e.g., diffuse fibrillary astrocytomas or oligodendrogliomas), which will increase the validity of the results.

## Conclusion

DKI parameters are significantly strongly correlated with the gliomas proliferative activity index. A statistically significant correlation has been observed between the gliomas proliferative activity and DKI parameters of the contralateral normal appearing white matter. DKI demonstrated high sensitivity in detection of microstructural changes that occur with increasing malignancy of gliomas both in the tumor and in the unaltered, according to standard MRI, brain structures.

**Authors declare no conflict of interest.**

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## Commentary

The research conducted by the authors and the results presented in the article have great scientific novelty and are extremely relevant. The authors used a novel diagnostic technique, diffusion kurtosis imaging, which has a number of advantages over the diffusion tensor MRI and allow determination of not only the flow rate of molecular diffusion, but also, importantly, quantification of the resistance to molecular diffusion in different directions. The work is original, because the authors were the first ones to use diffusion kurtosis imaging in the diagnosis of gliomas degree of malignancy based on the Ki-67/MIB-1 labeling index of glial brain tumors. Neuroimaging, pathological and immunohistochemical correlations are described in detail and their basics are analyzed for brain gliomas with different degrees of malignancy and the use of DKI.

The obvious novelty of this work is the identification of structural changes that the authors observed in the contralateral hemisphere of the brain with an increase in Ki-67/MIB-1 labeling index of the glial brain tumors. The authors suggest that changes in the contralateral hemisphere may be due to increased proliferation of the glia in patients with high values of Ki-67/MIB-1 LI of the glial tumor in contrast to patients with lower values of Ki-67/MIB-1 LI of the tumor. The authors believe that these data support the hypothesis that glial tumors are diseases of the entire brain, rather than local tumor pathological processes.

Clinical and radiographic studies convincingly demonstrate high efficiency of DKI in the diagnosis of degree of brain gliomas malignancies; the new method of neuroimaging undoubtedly has great diagnostic potential.

The fundamental provisions elucidated by the authors are objectively supported by the presented material, have fundamental innovative value and represent the basis for further research on the objectification of diagnostic of glial tumors degree of malignancy during preoperative stage.

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