Acute changes in diffusion tensor-derived metrics and its correlation with the motor outcome in gliomas adjacent to the corticospinal tract

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Abstract

Background: This study involves analysis of the relationship between variables obtained using diffusion tensor imaging (DTI) and motor outcome in gliomas adjacent to the corticospinal tract (CST).

Methods: Histologically confirmed glioma patients who were to undergo surgery between January 2018 and December 2019 were prospectively enrolled. All patients had a preoperative magnetic resonance imaging (MRI) study that included DTI, a tumor 2 cm or less from the CST, and postsurgical control within 48 h. Patients with MRI that was performed at other center, tumors with primary and premotor cortex invasion, postsurgical complications directly affecting motor outcome and tumor progression <6 months were excluded in the study. In pre- and post-surgical MRI, we measured the following DTI-derived metrics: fractional anisotropy (FA), mean diffusivity, axial diffusivity, and radial diffusivity of the entire CST and peritumoral CST regions and in the contralateral hemisphere. The motor outcome was assessed at 1, 3, and 6 months using the Medical Research Council scale.

Results: Eleven patients were analyzed, and six corresponded to high-grade gliomas and five to low-grade gliomas. Four patients had previous motor impairment and seven patients had postsurgical motor deficits (four transient and three permanent). An FA ratio of 0.8 between peritumoral CST regions and the contralateral hemisphere was found to be the cutoff, and lower values were obtained in patients with permanent motor deficits.

Conclusion: Quantitative analysis of DTI that was performed in the immediate postsurgery period can provide valuable information about the motor prognosis after surgery for gliomas near the CST.

Keywords: Corticospinal tract, Diffusion tensor imaging, Fiber tracking, Glioma, Motor outcome

Introduction

Gliomas are neoplasms that are characterized by their ability to extend through white matter (WM) tracts compromising structures that are involved in movement, language, and cognition. Gliomas located near the corticospinal tract (CST) are a surgical challenge because of the proximity between the borders of the resection and important structures that may lead to neurosurgical deficits. Surgery on these tumors has reached a high level of technological complexity, using tools such as intraoperative fluorescence, neuronavigation, and neurophysiological monitoring.8,33,37
The motor cortex is divided into the primary motor cortex, premotor cortex, cingulate motor area, and supplementary motor area. The CST is the main pathway that is involved in voluntary movement control. Pyramidal neurons of the primary motor cortex form the CST, which also receives fibers from the accessory motor areas, and from the parietal/somatosensory cortex.[11]

Diffusion tensor imaging (DTI) is a non-invasive magnetic resonance imaging (MRI) technique that measures the anisotropic diffusion of water molecules. WM tractography, which is also known as fiber tracking, allows a three-dimensional visualization of WM tracts. In addition, the architecture and integrity of WM fascicles can be assessed using a mathematical model that is composed of eigenvalues ($\lambda$) and eigenvectors ($\varepsilon$) by which the displacement of the water molecule signal within a voxel is characterized.[3-5,15,27,28,32] In addition, quantitative information on DTI can be used to assess the degree of invasion or infiltration of the WM[16,33] and the CST.[20,45] The quantitative analysis of DTI through its derived metrics may reflect the effects of the tumor on the surrounding WM, allowing, for example, analysis of how gliomas change the microstructural integrity of the main WM tracts. In the WM, water molecules diffuse more rapidly along the fibers and more slowly perpendicular to them, which is called anisotropic diffusion.[11] The following four coefficients or scalars can be extracted from the DTI: axial diffusivity (AD), which represents the diffusivity along the direction of dominant diffusion, radial diffusivity (RD), which represents the average diffusivity perpendicular to the first eigenvector, mean diffusivity (MD), which describes the magnitude of the diffusion, and fractional anisotropy (FA), which describes the degree of anisotropy. These metrics provide information about the state of the WM tracts and may also suggest specific types of neuronal damage such as axonal injury, demyelination, inflammation, or necrosis.[2,10,13,24,36,39]

Several publications have studied the acute diffusivity changes in WM and selected regions of the CST in patients early after a stroke. A relationship between decreased anisotropic diffusivity and worse motor outcome has been described.[17,18,35,44]

For brain tumors, there are few studies that use DTI as a prognostic tool for motor function.[23,49] To the best of our knowledge, this is the first study that aims to quantitatively analyze the DTI information that was obtained in the immediate postsurgical period (within 48 h). The objective is to find a correlation with the motor outcome in surgical excised gliomas. The secondary objective is to establish a cutoff point based on the tensor metrics that allow identification of patients who will develop a permanent postsurgical motor deficit.

MATERIALS AND METHODS

We prospectively enrolled histologically confirmed glioma patients who were to undergo surgery in our department between January 2018 and December 2019. All patients had a preoperative MRI study that included DTI. We included patients in whom the tumor was located 2 cm or less from the CST and who had postsurgical MRI control within 48 h. The surgeries were performed in a standardized manner using microsurgical techniques, neuronavigation, neurophysiological monitoring, and intraoperative ultrasound.

We excluded patients with MRI that was performed at other centers, tumors that invaded the primary motor cortex, supplementary motor area, and premotor cortex, and patients who had postsurgical complications with a direct impact on motor outcome (hematomas or ischemia). Stereotactic biopsies and patients with tumor progression for <6 months that were demonstrated in control MRI studies were also excluded from the study.

The clinical and radiological variables are summarized in [Table 1]. Motor function was assessed using the Medical Research Council (MRC) scale, with scores ranging from 0 to 5.[61] Using this scale, the presence or absence of pre- and post-surgical motor deficits was determined. In the postsurgical period, patients were assessed in the 1st week, at 1–3 and 6 months. A permanent deficit was defined as a deficit that persisted for 3 months after surgery.

Image acquisition protocol

All subjects were scanned using a 1.5 T MRI scanner (Signa HDxt; GE Healthcare, Milwaukee, WI, USA). DTI data were acquired using a single shot echo-planar imaging sequence (TE, 96 ms; TR, 13675 ms; field of view, 256 × 256 mm; matrix size, 128 × 128; voxel size, 1.015 × 1.015 × 3 mm). The diffusion-weighting gradient was applied in 25 isotropically distributed directions using a b value of 1000 s/mm². Fifty gapless slices were obtained to cover the whole brain, with a thickness of 3 mm. The total DTI acquisition time was approximately 4 min. The b-table was checked by an automatic quality control routine to ensure its accuracy.[48] Conventional MR sequences T1, T2-weighted imaging, fluid attenuated inversion recovery (FLAIR), and specific neuronavigation images were also acquired.

Imaging analysis and fiber tracking

Fiber tracking was performed with a deterministic algorithm using DSI Studio (dsi-studio.labsolver.org).[47] We used a FA threshold of 0.15, angulation threshold of 50°, and minimum fiber length of 50 mm. Diffusion coefficient (FA, MD, AD, and RD) maps were automatically obtained for each patient.
CST was reconstructed using the regions of interest (ROIs) that were located at the midbrain, posterior limb of internal capsule, and primary motor cortex [Figure 1].[43] Using manual tools, fibers that were not anatomically related to the tract were removed (contralateral hemisphere, cerebellum, or thalamus). Volumetric tools (Elements [Brainlab AG, Feldkirchen, Germany]) were used to calculate tumor volume based on preoperative MRI. The minimum distance between the CST and the tumor was measured. In all cases, the contralateral CST was reconstructed after ensuring that there were no alterations in the hemisphere contralateral to the lesion. Using the color map and coregistered T1 and T2-FLAIR images, ROIs (diameter = 8 mm) were drawn in the region of the CST that was closest to the tumor and its mirror image in the healthy hemisphere [Figure 2]. The different metrics derived from the tensor were obtained for the entire CST and the peritumoral regions of the ipsilateral and contralateral tract. We also calculated their ratio, as follows: ipsilateral (affected)/contralateral (healthy).

### Table 1: Patient characteristics.

| Variable                              | n   |
|---------------------------------------|-----|
| Age                                   | 49.82±14.34 |
| Sex                                   |     |
| Female                                | 5 (45.5%) |
| Male                                  | 6 (55.5%) |
| Preoperative KPS (IQR)                | 80 (20) |
| Histopathology                        |     |
| High-grade gliomas                    | 5 (45.5%) |
| Glioblastoma                          | 1 (9.1%) |
| Anaplastic astrocytoma Grade III      |     |
| Low-grade gliomas                     | 1 (9.1%) |
| Astrocytoma Grade II                  | 4 (36.4%) |
| Oligodendroglioma Grade II            |     |
| Tumor location                        |     |
| Frontal                               | 7 (63.6%) |
| Parietal                              | 1 (9.1%) |
| Temporal                              | 1 (9.1%) |
| Insular                               | 2 (18.2%) |
| Initial volume (cm³)                  | 43.32±33.01 |
| Type of resection                     |     |
| PR                                    | 2 (18.2%) |
| STR                                   | 2 (18.2%) |
| GTR                                   | 7 (63.6%) |
| CST compromise                        |     |
| None                                  | 4 (36.4%) |
| Displaced                             | 4 (36.4%) |
| Infiltrated/Disrupted                 | 3 (27.3%) |
| Days between preoperative MRI and surgery (IQR) | 1 (6) |
| Preoperative motor score (MCR)        |     |
| Upper limb                            |     |
| 3                                     | 1 (9.1%) |
| 5                                     | 10 (90.9%) |
| Lower limb                            |     |
| 4                                     | 3 (27.3%) |
| 5                                     | 8 (72.7%) |
| Postoperative motor score (MCR) at 6th month |     |
| Upper limb                            |     |
| 3                                     | 1 (9.1%) |
| 4                                     | 2 (18.2%) |
| 5                                     | 8 (72.7%) |
| Lower limb                            |     |
| 0                                     | 1 (9.1%) |
| 3                                     | 1 (9.1%) |
| 4                                     | 1 (9.1%) |
| 5                                     | 8 (9.1%) |

Values are expressed as the mean±standard deviation or as the frequency (%). KPS: Karnofsky Performance Score, MRC: Medical Research Council, IQR: Interquartile range, CST: Corticospinal tract, PR: Partial resection, STR: Subtotal resection, GTR: Gross total resection

### Statistical analysis

A normality test was applied to the sample using the Shapiro–Wilk test. Variables that were derived from the tensor had a non-normal distribution. The DTI values were compared with the presence of a preoperative deficit using the Wilcoxon–Mann–Whitney test, calculating the U statistic and the effect size with the r coefficient. The postsurgical motor status that was represented by the categories “no deficit,” “transient deficit,” and “permanent deficit” was compared with the tensor metrics using the Kruskal–Wallis test, using the epsilon squared (ε²) coefficient as a measure of the effect size. A post hoc study was also performed using the Holm correction and the Wilcoxon rank-sum test.

The medians of the tensor values were also analyzed according to the presence or absence of motor impairment, comparing the ipsilateral to the contralateral values in both pre- and post-operative MRI. Thus, we used the Wilcoxon signed-rank test. All statistical analyses were performed in R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

### RESULTS

During the study period, 53 patients with histologically confirmed glioma underwent surgical resection. Fourteen patients met the criteria of proximity to the CST. Three patients were excluded because of motor/premotor cortex invasion, postsurgical primary motor cortex infarction, or DTI performed at another center. Thus, 11 patients met the selection criteria and were included in the analysis.

Six (55.5%) patients were men and five (45.5%) patients were women. The mean age was 49.82 ± 14.34 years, the median presurgical Karnofsky performance scale (KPS) was 80 (20). Six were high-grade and five were low-grade gliomas. The mean initial volume was 43.32 ± 33.1 cm³. Four patients presented a presurgical motor deficit and the motor balance is summarized in [Table 1]. Three patients who presented a
previous deficit showed worsening of their motor balance postoperatively [Figure 3], and one of the patients with a previous deficit improved after the intervention. In four patients, new postsurgical deficits were observed, and all of them were transient motor deficits. Significant alterations were observed during intraoperative neurophysiological monitoring in three patients (27.7%), with a reduction in MEP amplitude. Two of these patients had a permanent motor deficit. The third patient with a permanent motor deficit did not register alterations during neurophysiological monitoring, presumably due to a technical failure.

The presence of a permanent motor deficit was not correlated with the clinical or radiological variables including initial tumor volume, extent of resection, and distance to the CST. Although the three patients with a permanent deficit corresponded to high-grade gliomas, this relationship did not reach statistical significance. [Supplementary Table 1] shows descriptive statistics for the pre- and post-operative DTI values in the overall study sample.

Quantitative analysis of the tensor metrics is summarized in [Supplementary Tables 2 and 3]. In patients without motor impairment, there were no differences between the overall CST values on the affected and contralateral sides in the pre- and post-surgical studies. However, in the peritumoral regions, the values of FA, MD, and RD were significantly different in patients who had a motor deficit.

[Supplementary Table 4] shows the relationship between the tensor values and the presence of a preoperative deficit. The peritumoral regions and their ratio exhibited significantly lower FA values in cases of deficit, while the MD and RD values were higher.

The results of the postoperative DTI and motor outcome analyses are shown in [Table 2] and [Figure 4]. There were differences between the MD values of overall CST between the groups (H= 6.96, df = 2, P = 0.031, ε² = 0.70), and the difference between the groups with non-deficit and permanent deficit was statistically significant (Z =2.42, P = 0.047, r = 0.66). In the peritumoral regions, there were differences between the values of FA, MD, and RD. For
the ratios, only the rFA showed a significantly different distribution ($H = 7.48, df = 2, P = 0.24, \epsilon^2 = 0.75$), and this difference was statistically significant between the cohorts with and without permanent deficit ($Z = 2.65, P < 0.001, r = 0.80$). Although the median values for the FA ratio in patients with permanent motor deficits were lower (0.77) compared to patients with transient deficits (0.88), these differences did not reach statistical significance ($P = 0.331$).

A cutoff based on the receiver operating characteristic curves was calculated, establishing a threshold value of 0.8 for the rFA, and thus, lower values are related to the presence of a permanent motor deficit in our series [Supplementary Table 5 and Figure 5].

**DISCUSSION**

In the present study, we implemented DTI quantitatively to elucidate the relationship between the clinical outcome and this radiological-derived information. Among the main findings of this investigation, patients who presented a postsurgical motor deficit had lower FA and higher MD and RD values compared to patients who did not show any deficit.

Among the strengths of our study, our results rely on DTI studies that were performed within the first 48 postoperative h. In addition, the analysis and image processing focus on the CST regions that are adjacent to the tumor and surgical cavity, and these areas are susceptible to postsurgical changes. Qualitative representation of the variable of interest (motor outcome) simplifies the analysis and its interpretation.

We established an objective definition of the tumor’s proximity to the CST based on previous publications. We discarded cases that may bias the analysis of the results, such as tumors that had invaded the motor and premotor cortex, because the damage in these areas could lead to motor impairments that do not directly involve the CST.

**Figure 3:** Illustrative cases of permanent motor deficits. From left to right: preoperative T1-weighted postcontrast and postoperative images: T1-weighted postcontrast, diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) map. The location of the pyramidal tract that was determined by fiber tracking is also shown (white asterisk). (a) A 53-year-old man with a parieto-temporal glioblastoma; (b) a 65-year-old man with a right frontal glioblastoma; and (c) a 54-year-old man with a right temporo-insular glioblastoma.
### Table 2: Univariate analysis between quantitative DTI-derived metrics and postoperative motor deficit.

| Variable                      | DTI metric | Postoperative deficit | Kruskal–Wallis test | Post hoc Dunn test | Wilcoxon rank sum test |
|-------------------------------|------------|------------------------|----------------------|--------------------|------------------------|
|                               |            | No (n=4)               | Yes                  |                    |                        |
|                               |            | Transient (n=4)        | Permanent (n=3)      |                    |                        |
| Overall CST                   | FA         | 0.60 (0.04)            | 0.57 (0.06)          | 0.55 (0.02)        | 3.55                   |
|                               | MD         | 0.84 (0.02)            | 0.90 (0.03)          | 0.93 (0.02)        | 6.96                   |
|                               | AD         | 1.45 (0.05)            | 1.50 (0.05)          | 1.50 (0.04)        | 1.19                   |
|                               | RD         | 0.54 (0.03)            | 0.62 (0.07)          | 0.64 (0.01)        | 5.86                   |
| Peritumoral CST region        | FA         | 0.67 (0.07)            | 0.49 (0.01)          | 0.49 (0.15)        | 7                      |
|                               | MD         | 0.75 (0.03)            | 0.99 (0.25)          | 0.96 (0.18)        | 6.54                   |
|                               | AD         | 1.38 (0.09)            | 1.62 (0.42)          | 1.54 (0.09)        | 2.1                    |
|                               | RD         | 0.43 (0.02)            | 0.68 (0.16)          | 0.67 (0.23)        | 7.1                    |
| Ratio ipsilateral/contralateral | rFA      | 0.98 (0.03)            | 0.92 (0.07)          | 1.02 (0.05)        | 5.21                   |
|                               | rMD        | 1.05 (0.04)            | 1.04 (0.07)          | 1.01 (0.01)        | 1.53                   |
| Overall CST                   | rAD        | 1.02 (0.03)            | 0.98 (0.04)          | 1.03 (0.03)        | 3.45                   |
|                               | rRD        | 1.08 (0.07)            | 1.10 (.13)           | 0.98 (0.03)        | 2.27                   |
| Ratio Ipsilateral/Contralateral | rFA      | 1.02 (.10)             | 0.88 (0.17)          | 0.77 (0.16)        | 7.48                   |
| Peritumoral CST region        | rMD        | 0.99 (0.14)            | 1.28 (0.26)          | 1.19 (0.23)        | 3.3                    |
|                               | rAD        | 0.99 (0.15)            | 1.21 (0.20)          | 1.05 (0.15)        | 3.61                   |
|                               | rRD        | 1 (0.15)               | 1.38 (0.34)          | 1.59 (0.25)        | 5.63                   |

Values are expressed as the median and IQR (interquartile range). CST: Corticospinal tract, PERM: Permanent, TRANS: Transient. DTI values are expressed in $10^{-3}$ mm$^2$/s.
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We emphasize the importance of standardizing MRI acquisition and postprocessing imaging, especially the time at which the postoperative control study is performed. Other studies that correlated MRI data with the motor outcome are based on preoperative studies\cite{9,14,19,40} that provide limited prognostic information. In our series, we also distinguished patients with transient postoperative motor deficits from those with permanent deficits.

The robustness of our methodology relies on the addition of a quantitative, comparative analysis based on data that were derived from pre and postoperative DTI. Most of previous studies had methodologies that often disregarded this important information. In a study by Laundre et al.,\cite{23} in which qualitative analysis of DTI was performed using late postsurgical images, the author found an association between normalization of the position and anisotropy of the CST with

Figure 4: Box plots showing differences in the peritumoral diffusion tensor imaging-derived metrics according to the type of postoperative motor deficit. (a) Peritumoral fractional anisotropy (FA); (b) peritumoral mean diffusivity; (c) peritumoral radial diffusivity; and (d) p FA ratio (rFA; affected/unaffected).

Figure 5: Graphic output of cutoff determination using the Youden index. (a) Metric values by the optimal criterion. (b) Cutoff point for peritumoral FA ratio (rFA; affected/unaffected). AUC: Area under the curve.
a clinical improvement of postoperative motor function. In a study by Yuanzheng et al.,[40] intraoperative tractography was used, establishing the distance from the postsurgical cavity to the CST as a risk factor for the appearance of postoperative deficits, and the author did not use any quantitative parameters. Roberts et al.[36] used the fiber density index as a measure of the number of fibers (NFs) that are measured in a transverse ROI of the tract, which provides a semi-quantitative study parameter, although it is not an absolute measure. Similarly, Ius et al.[19] assessed the NF index, and they found significant differences between the ipsilesional and contralateral NF. In that series, a NF value <0.22 in the preoperative DTI study was correlated with a low probability of developing a transient postsurgical deficit. Yao et al.[46] sought to determine the prognostic value of DTI in brainstem surgery using FA and ADC values and a laterality index. The consistency of those study methods can be improved because only seven of 14 patients had a postsurgical DTI, and none of them presented deficits postoperatively. Similarly, Abhinav et al.[1] studied the relationship between the degree of muscular strength and the presurgical DTI metrics, and in his series of deep intracranial cavernous malformations, only nine of 18 patients underwent postoperative study.

In a study by Gao et al.,[14] based on the preoperative DTI, the author performed his measurement on the posterior limb of the internal capsule, he used the absolute value of FA and the tumoral-to-healthy FA ratio, as well as the FDI and the FDI ratios. In this study, the authors found a positive correlation between muscular strength and rFA and between FDI and rFDI. However, it seems that the most important differences occur in the regions of the tract near the tumor. As shown by D’Souza et al.[9] and Stadlbauer et al.,[40-42] these changes mainly consist of a decrease in FA and an increase in MD with respect to the contralateral hemisphere. Other research in the field of stroke corroborates these trends.[17,22,29,35]

In our series, the tensor metrics of the preoperative studies in which the entire CST is measured are similar for both the ipsilesional and contralateral healthy hemisphere. The values are similar to the series described by Cosottini et al.,[7] Roberts et al.,[36] and Stadlbauer et al.[40] For the postoperative study, the only value of the entire CST that is significantly different between patients who do not have postoperative deficits and those with permanent deficits was the increase in MD (0.84 vs. 0.93 × 10⁻³ mm²/s, P = 0.047, Z = 2.42, r = 0.66).

The most important differences have been found when studying the CST regions that are adjacent to the tumor and the postsurgical cavity. We showed that in these areas, patients who presented with a postsurgical motor deficit had lower FA and higher values of MD and RD compared to patients who did not show any deficit. Doughty et al.[12] showed that reduced FA is found in the first 3–4 days after a stroke only when the ROI was very close to the ischemic lesion, but not when the ROI was further away, and because of Wallerian degeneration, it took time to become established.[12]

For the ratio between peritumoral CST areas and the contralateral hemisphere, rFA was significantly lower in patients with permanent deficits. Through ROC curve analysis, the threshold we set in our series of 0.8 was related to a permanent postoperative motor deficit, and this threshold value was similar to that described in papers that assessed motor outcome in patients after a stroke,[22,25-48] although the pathophysiological mechanisms could be different.

These regional variations of the CST can represent irreversible damage to the tract, which is also found in patients with transient deficits but with a different magnitude. Among the three patients with a permanent deficit in our series, all had a preoperative motor deficit, while the four patients with a new postoperative deficit presented peritumoral CST alterations. However, these values did not become significant for the group that did not present deficits. This suggests that alterations of the tensor metrics in this group may be related to surgical manipulation and displacement or decompression of the CST instead of structural damage, as would occur in patients with an irreversible deficit.

The study of early postsurgical DTI suggests that the presence of artifacts in the acquisition, the presence of blood, small areas of ischemia, or patient movements can make it difficult to reconstruct the pyramidal tract as well as the values that are derived from its analysis.

Our study has some limitations. These include a small study sample size; images acquired using a 1.5 T scanner, and the absence of long-term DTI controls that would allow us a longitudinal analysis of the tensor values and the motor outcomes.

Future studies should focus on validation of the present methodology and results with a larger prospective series. We believe that DTI can provide valuable prognostic information in glioma surgery near eloquent areas. Efforts should be directed toward the creation of predictive models based on DTI and clinical variables that allow identification of patients who have a high risk of permanent motor sequelae. However, if we can differentiate postsurgical alterations based on CST metrics, we can provide patients with transient deficits valuable information about its functional prognosis, potential recovery, and rehabilitation strategies. These image processing tools should evolve into user friendly software, and improvements in spatial resolution and tensor reconstruction techniques should help to overcome the current technical difficulties.

**CONCLUSION**

Quantitative DTI analysis that was performed in the immediate postsurgical period revealed changes in the CST area values near the tumor, which were consistently related...
to the motor outcome in our series. Our results showed that the peritumor-to-healthy FA ratio in the CST allows discrimination between patients who will and will not develop a permanent postoperative deficit.

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Declaration of patient consent

Institutional Review Board permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Abhinav K, Nielsen TH, Singh R, Weng Y, Han SS, Iv M, et al. Utility of a quantitative approach using diffusion tensor imaging for prognostication regarding motor and functional outcomes in patients with surgically resected deep intracranial cavernous malformations. Neurosurgery 2019;86:665-75.

2. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. Neurotherapeutics 2007;4:316-29.

3. Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. *In vivo* fiber tractography using DT-MRI data. Magn Reson Med 2000;44:625-32.

4. Berman JL, Berger MS, Chung S, Nagarajan SS, Henry RG. Accuracy of diffusion tensor magnetic resonance imaging tractography assessed using intraoperative subcortical stimulation mapping and magnetic source imaging. J Neurosurg 2007;107:488-94.

5. Clark CA, Barrick TR, Murphy MM, Bell BA. White matter fiber tracking in patients with space-occupying lesions of the brain: A new technique for neurosurgical planning? Neuroimage 2003;20:1601-8.

6. Compton A. Aids to the investigation of peripheral nerve injuries. medical research council: Nerve injuries research committee. His majesty's stationery office: 1942; pp. 48 (iii) and 74 figures and 7 diagrams; with aids to the examination of the peripheral nervous. Brain 2010;133:2838-44.

7. Cosottini M, Giannelli M, Siciliano G, Lazzarotti G, Michelassi MC, Del Corona A, et al. Diffusion-tensor MR imaging of corticospinal tract in amyotrophic lateral sclerosis and progressive muscular atrophy. Radiology 2005;237:258-64.

8. D'Andrea G, Angelini A, Romano A, di Lauro A, Sessa G, Bozzao A, *et al*. Intraoperative DTI and brain mapping for surgery of neoplasm of the motor cortex and the corticospinal tract: Our protocol and series in BrainSUITE. Neurosurg Rev 2012;35:401-12; discussion 412.

9. D’Souza S, Ormond DR, Costabile J, Thompson JA. Fiber-tract localized diffusion coefficients highlight patterns of white matter disruption induced by proximity to glioma. PLoS One 2019;14:e0225323.

10. Davanian F, Faeghi F, Shahzadi S, Farshifar Z. Diffusion tensor imaging for glioma grading: Analysis of fiber density index. Basic Clin Neurosci 2017;8:13-8.

11. Davidoff RA. The pyramidal tract. Neurology 1990;40:332-9.

12. Doughty C, Wang J, Feng W, Hackney D, Pani E, Schlaug G. Detection and predictive value of fractional anisotropy changes of the corticospinal tract in the acute phase of a stroke. Stroke 2016;47:1520-6.

13. Field AS, Alexander AL, Wu YC, Hasan KM, Witwer B, Badie B. Diffusion tensor eigenvector directional color imaging patterns in the evaluation of cerebral white matter tracts altered by tumor. J Magn Reson Imaging 2004;20:555-62.

14. Gao B, Shen X, Shiroishi MS, Pang M, Li Z, Yu B, et al. A pilot study of pre-operative motor dysfunction from gliomas in the region of corticospinal tract: Evaluation with diffusion tensor imaging. PLoS One 2017;12:e0182795.

15. Glenn OA, Henry RG, Berman JL, Chang PC, Miller SP, Vigneron DB, *et al*. DTI-based three-dimensional tractography detects differences in the pyramidal tracts of infants and children with congenital hemiparesis. J Magn Reson Imaging 2003;18:641-8.

16. Goebell E, Paustenbach S, Vaeterlein O, Ding XQ, Heese O, Fiehler J, et al. Low-grade and anaplastic gliomas: Differences in architecture evaluated with diffusion-tensor MR imaging. Radiology 2006;239:217-22.

17. Groisser BN, Copen WA, Singhal AB, Hirai KK, Schaechter JD. Corticospinal tract diffusion abnormalities early after stroke predict motor outcome. Neurorehabil Neural Repair 2014;28:751-60.

18. Imura T, Nagasawa Y, Inagawa T, Imada N, Izumi H, Emoto K, et al. Prediction of motor outcomes and activities of daily living function using diffusion tensor tractography in acute hemiparetic stroke patients. J Phys Ther Sci 2015;27:1383-6.

19. Ius T, Turella L, Pauletto G, Isola M, Maieron M, Sciacca G, et al. Quantitative diffusion tensor imaging analysis of low-grade gliomas: From preclinical application to patient care. World Neurosurg 2017;97:333-43.

20. Jeong JW, Lee J, Kamson DO, Chugani HT, Juhász C. Detection of hand and leg motor tract injury using novel diffusion tensor MRI tractography in children with central motor dysfunction. Magn Reson Imaging 2015;33:895-902.

21. Kallenberg K, Goldmann T, Menke J, Strik H, Bock HC, Stockhammer F, *et al*. Glioma infiltration of the corpus callosum: Early signs detected by DTI. J Neurooncol 2013;112:217-22.

22. Kusano Y, Seguchi T, Horiuchi T, Kakizawa Y, Kobayashi T, Tanaka Y, *et al.* Prediction of functional outcome in acute cerebral hemorrhage using diffusion tensor imaging at 3T: A prospective study. AJNR Am J Neuroradiol 2009;30:1561-5.

23. Laundre BJ, Jellison BJ, Badie B, Alexander AL, Field AS. Diffusion tensor imaging of the corticospinal tract before and after mass resection as correlated with clinical motor findings: Preliminary data. AJNR Am J Neuroradiol 2005;26:791-6.
24. Ma L, Song ZJ. Differentiation between low-grade and high-grade glioma using combined diffusion tensor imaging metrics. Clin Neurol Neurosurg 2013;115:2489-95.
25. Maeda T, Ishizaki K, Yura S. Can diffusion tensor imaging predict the functional outcome of supra-tentorial stroke? No To Shinkei 2005;57:27-32.
26. Maesawa S, Fujii M, Nakahara N, Watanabe T, Wakabayashi T, Yoshida J. Intraoperative tractography and motor evoked potential (MEP) monitoring in surgery for gliomas around the corticospinal tract. World Neurosurg 2010;74:153-61.
27. Mori S, Crain BJ, Chacko VP, van Zijl PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol 1999;45:265-9.
28. Mori S, Kaufmann WE, Davatzikos C, Stelitjes B, Amodio L, Frederiksen K, et al. Imaging cortical association tracts in the human brain using diffusion-tensor-based axonal tracking. Magn Reson Med 2002;47:215-23.
29. Moulton E, Magno S, Valabregue R, Amor-Sahli M, Pires C, Lehericy S, et al. Acute diffusivity biomarkers for prediction of motor and language outcome in mild-to-severe stroke patients. Stroke 2019;50:2050-6.
30. Moura LM, Luccas R, de Paiva JP, Amaro E, Leemans A, Leite CC, et al. Diffusion tensor imaging biomarkers to predict motor outcomes in stroke: A narrative review. Front Neurol 2019;10:445.
31. Mukherjee P, Berman JI, Chung SW, Hess CP, Henry RG. Diffusion tensor MR imaging and fiber tractography: Theoretic underpinnings. AJNR Am J Neuroradiol 2008;29:632-41.
32. Nimsky C, Ganslandt O, Merhof D, Sorensen AG, Fahlbusch R. Intraoperative visualization of the pyramidal tract by diffusion-tensor-based fiber tracking. Neuroimage 2006;30:1219-29.
33. Noell S, Feigl GC, Naros G, Barking S, Tatagiba M, Ritz R. Experiences in surgery of primary malignant brain tumours in the primary sensori-motor cortex practical recommendations and results of a single institution. Clin Neurol Neurosurg 2015;136:41-50.
34. Plans G, Fernández-Concejero I, Rifá-Ros X, Fernández-Coello A, Rosselló A, Gabarrós A. Evaluation of the high-frequency monopolar stimulation technique for mapping and monitoring the corticospinal tract in patients with supratentorial gliomas. A proposal for intraoperative management based on neurophysiological data analysis in a series of 92 patients. Neurosurgery 2017;81:585-94.
35. Puig J, Pedraza S, Blasco G, Daunis-I-Estadella J, Prados F, Remolli S, et al. Acute damage to the posterior limb of the internal capsule on diffusion tensor tractography as an early imaging predictor of motor outcome after stroke. AJNR Am J Neuroradiol 2011;32:857-63.
36. Roberts TPL, Liu F, Kassner A, Mori S, Guha A. Fiber density index correlates with reduced fractional anisotropy in white matter of patients with glioblastoma. AJNR Am J Neuroradiol 2005;26:2183-6.
37. Rossetto M, Ciccarino P, Lombardi G, Rolma G, Cecchin D, Puppa AD. Surgery on motor area metastasis. Neurosurg Rev 2016;39:71-7; discussion 77-8.
38. Schilling KG, Gao Y, Li M, Wu TL, Blaber J, Landman BA, et al. Functional tractography of white matter by high angular resolution functional-correlation imaging (HARFI). Magn Reson Med 2019;81:2011-24.
39. Sinha S, Bastin ME, Whittle IR, Wardlaw JM. Diffusion tensor MR imaging of high-grade cerebral gliomas. AJNR Am J Neuroradiol 2002;23:520-7.
40. Stadlbauer A, Nimsky C, Gruber S, Moser E, Hammen T, Engelhorn T, et al. Changes in fiber integrity, diffusivity, and metabolism of the pyramidal tract adjacent to gliomas: A quantitative diffusion tensor fiber tracking and MR spectroscopic imaging study. AJNR Am J Neuroradiol 2007;28:462-9.
41. Stadlbauer A, Hammen T, Grummich P, Buchfelder M, Kuwert T, Dorfler A, et al. Classification of peritumoral motor tract alterations in gliomas using metabolic and structural neuroimaging. J Nucl Med 2011;52:1227-34.
42. Stadlbauer A, Nimsky C, Buslei R, Salomonowitz E, Hammen T, Buchfelder M, et al. Diffusion tensor imaging and optimized fiber tracking in glioma patients: Histopathologic evaluation of tumor-invaded white matter structures. Neuroimage 2007;34:949-56.
43. Wakana S, Caprihan A, Panzenboeck MM, Fallon JH, Perry M, Gollub RL, et al. Reproducibility of quantitative tractography methods applied to cerebral white matter. Neuroimage 2007;36:630-44.
44. Wang DM, Li J, Liu JR, Hu HY. Diffusion tensor imaging predicts long-term motor functional outcome in patients with acute supratentorial intracranial hemorrhage. Cerebrovasc Dis 2012;34:199-205.
45. Wittwer BP, Moftakharr F, Hasan KM, Deshmukh P, Haughton V, Field A, et al. Diffusion-tensor imaging of white matter tracts in patients with cerebral neoplasm. J Neurosurg 2002;97:568-75.
46. Yao Y, Ulrich NH, Guggenberger R, Alzarhani YA, Bertalanffy H, Kollias SS. Quantification of corticospinal tracts with diffusion tensor imaging in brainstem surgery: Prognostic value in 14 consecutive cases at 3T magnetic resonance imaging. World Neurosurg 2015;83:1006-14.
47. Yeh FC, Verstynen TD, Wang Y, Fernández-Miranda JC, Tseng WY. Deterministic diffusion fiber tracking improved by quantitative anisotropy. PLoS One 2013;8:e80713.
48. Yoshioka H, Horikoshi T, Aoki S, Hori M, Ishigame K, Uchida M, et al. Diffusion tensor tractography predicts motor functional outcome in patients with spontaneous intracerebral hemorrhage. Neurosurgery 2008;62:97-103; discussion 103.
49. Yuanzheng H, Lichao M, Xiaolei C, Bainan X. Functional outcome of surgery for glioma directly adjacent to pyramidal tract depicted by diffusion-tensor based fiber tracking. Turk Neurosurg 2015;25:438-45.
### SUPPLEMENTARY TABLES

#### Supplementary Table 1: Descriptive statistics of quantitative DTI-derived metrics.

| Variable                        | DTI metric | Preoperative | Postoperative |
|---------------------------------|------------|--------------|---------------|
|                                 |            | Median | IQR | CI 95% | Median | IQR | CI 95% |
| Overall CST Ipsilateral         | FA         | 0.56  | 0.04 | 0.53–0.58 | 0.57  | 0.04 | 0.54–0.6 |
|                                 | MD         | 0.88  | 0.12 | 0.82–0.96 | 0.9   | 0.06 | 0.84–0.93 |
|                                 | AD         | 1.47  | 0.14 | 1.39–1.58 | 1.49  | 0.07 | 1.44–1.52 |
|                                 | RD         | 0.6   | 0.11 | 0.54–0.65 | 0.59  | 0.09 | 0.54–0.64 |
| Overall CST contralateral       | FA         | 0.56  | 0.03 | 0.55–0.58 | 0.58  | 0.07 | 0.55–0.63 |
|                                 | MD         | 0.88  | 0.07 | 0.85–0.92 | 0.87  | 0.08 | 0.83–0.93 |
|                                 | AD         | 1.47  | 0.09 | 1.43–1.54 | 1.48  | 0.1  | 1.41–1.51 |
|                                 | RD         | 0.59  | 0.09 | 0.58–0.64 | 0.58  | 0.1  | 0.51–0.62 |
| Peritumoral                     | FA         | 0.44  | 0.28 | 0.33–0.65 | 0.58  | 0.16 | 0.46–0.64 |
|                                 | MD         | 0.95  | 0.37 | 0.68–1.16 | 0.81  | 0.25 | 0.75–1.07 |
|                                 | AD         | 1.47  | 0.24 | 1.33–1.71 | 1.44  | 0.22 | 1.37–1.61 |
|                                 | RD         | 0.73  | 0.44 | 0.39–0.87 | 0.51  | 0.25 | 0.43–0.71 |
| Healthy CST region              | FA         | 0.64  | 0.20 | 0.51–0.74 | 0.61  | 0.12 | 0.56–0.69 |
|                                 | MD         | 0.72  | 0.06 | 0.70–0.76 | 0.77  | 0.05 | 0.74–0.80 |
|                                 | AD         | 1.31  | 0.29 | 1.11–1.46 | 1.39  | 0.13 | 1.31–1.46 |
|                                 | RD         | 0.44  | 0.17 | 0.34–0.53 | 0.44  | 0.08 | 0.41–0.51 |
| Ratio ipsilateral/contralateral | rFA        | 0.97  | 0.06 | 0.95–1.04 | 0.98  | 0.07 | 0.94–1.02 |
| Overall CST                     | rMD        | 1.01  | 0.05 | 0.95–1.02 | 1.03  | 0.05 | 1.00–1.05 |
|                                 | rAD        | 1     | 0.02 | 0.99–1.01 | 1.01  | 0.05 | 0.97–1.03 |
|                                 | rRD        | 1.02  | 0.09 | 0.9–1.03  | 1.08  | 0.12 | 0.97–1.09 |
| Ratio                           | rFA        | 0.92  | 0.27 | 0.71–0.99 | 0.93  | 0.22 | 0.77–1.01 |
| Ipsilateral/Contralateral       | rMD        | 1.34  | 0.51 | 1–1.59    | 1.19  | 0.29 | 1.01–1.34 |
| Peritumoral CST region          | rAD        | 1.12  | 0.29 | 0.96–1.34 | 1.05  | 0.02 | 0.94–1.24 |
|                                 | rRD        | 1.45  | 0.64 | 1.08–1.78 | 1.37  | 0.58 | 0.98–1.59 |

IQR: Interquartile range, CST: Corticospinal tract. DTI values are expressed in $10^{-3}$ mm$^2$/s.
### Supplementary Table 2: Quantitative analysis of preoperative DTI.

| Variable | DTI metric | Whole sample ($n=11$) | Motor deficit |
|----------|------------|------------------------|---------------|
|          |            | Ipsilateral | Contralateral | W  | P  | Ipsilateral | Contralateral | W  | P  | Ipsilateral | Contralateral | W  | P  |
| Overall CST | FA         | 0.56 (0.04) | 0.56 (0.03) | 43 | 0.259 | 0.56 (0.03) | 0.57 (0.03) | 21.5 | 0.747 | 0.53 (0.01) | 0.56 (0.02) | 3  | 0.180 |
|           | MD         | 0.88 (0.12) | 0.88 (0.07) | 64 | 0.843 | 0.92 (0.11) | 0.92 (0.05) | 22.5 | 0.847 | 0.88 (0.05) | 0.86 (0.03) | 12.5 | 0.240 |
|           | AD         | 1.47 (0.14) | 1.47 (0.09) | 58.5 | 0.921 | 1.48 (0.12) | 1.49 (0.07) | 20.5 | 0.654 | 1.43 (0.07) | 1.43 (0.02) | 8  | 1   |
|           | RD         | 0.6 (0.11)  | 0.59 (0.09) | 66 | 0.742 | 0.64 (0.11) | 0.62 (0.06) | 23  | 0.898 | 0.6 (0.04) | 0.58 (0.03) | 13  | 0.189 |
| Peritumoral CST region | FA | 0.44 (0.28) | 0.64 (0.20) | 32 | 0.066 | 0.64 (0.25) | 0.64 (0.22) | 20  | 0.609 | 0.34 (0.11) | 0.63 (0.12) | 0   | 0.029 |
|           | MD         | 0.95 (0.37) | 0.72 (0.06) | 89 | 0.065 | 0.81 (0.27) | 0.72 (0.04) | 29  | 0.607 | 1.18 (0.23) | 0.73 (0.06) | 16  | 0.027 |
|           | AD         | 1.47 (0.24) | 1.31 (0.29) | 93 | 0.034 | 1.43 (0.18) | 1.31 (0.22) | 34  | 0.249 | 1.62 (0.2)  | 1.34 (0.3)  | 14  | 0.114 |
|           | RD         | 0.73 (0.44) | 0.44 (0.17) | 92 | 0.042 | 0.46 (0.36) | 0.44 (0.19) | 26.5 | 0.443 | 0.96 (0.42) | 0.43 (0.06) | 16  | 0.023 |

Values are expressed as the median and IQR (interquartile range). CST: Corticospinal tract. DTI values are expressed in $10^{-3}$ mm$^2$/s.

### Supplementary Table 3: Quantitative analysis of postoperative DTI.

| Variable | DTI metric | Whole sample ($n=11$) | Motor deficit |
|----------|------------|------------------------|---------------|
|          |            | Ipsilateral | Contralateral | W  | P  | Ipsilateral | Contralateral | W  | P  | Ipsilateral | Contralateral | W  | P  |
| Overall CST | FA         | 0.57 (0.05) | 0.58 (0.07) | 51.5 | 0.575 | 0.60 (0.04) | 0.61 (0.07) | 7   | 0.884 | 0.55 (0.05) | 0.56 (0.07) | 19  | 0.522 |
|           | MD         | 0.90 (0.06) | 0.87 (0.08) | 72  | 0.468 | 0.84 (0.02) | 0.82 (0.05) | 11  | 0.465 | 0.9 (0.04) | 0.88 (0.07) | 33.5 | 0.272 |
|           | AD         | 1.49 (0.07) | 1.48 (0.10) | 63  | 0.895 | 1.45 (0.05) | 1.44 (0.08) | 8.5 | 1   | 1.5 (0.04) | 1.51 (0.09) | 22  | 0.797 |
|           | RD         | 0.59 (0.09) | 0.58 (0.09) | 72.5 | 0.448 | 0.54 (0.03) | 0.52 (0.07) | 9   | 0.884 | 0.64 (0.03) | 0.62 (0.08) | 32  | 0.368 |
| Peritumoral CST region | FA | 0.58 (0.16) | 0.61 (0.12) | 41  | 0.211 | 0.67 (0.07) | 0.66 (0.11) | 9.5  | 0.772 | 0.49 (0.10) | 0.61 (0.08) | 5.5  | 0.018 |
|           | MD         | 0.81 (0.25) | 0.77 (0.05) | 87  | 0.087 | 0.75 (0.03) | 0.76 (0.08) | 7.5  | 1   | 0.96 (0.26) | 0.78 (0.03) | 46.5 | 0.008 |
|           | AD         | 1.44 (0.22) | 1.39 (0.13) | 78  | 0.264 | 1.38 (0.09) | 1.36 (0.08) | 8   | 1   | 1.54 (0.27) | 1.4 (0.10) | 36  | 0.159 |
|           | RD         | 0.51 (0.25) | 0.44 (0.08) | 88.5 | 0.070 | 0.43 (0.02) | 0.43 (0.09) | 8   | 1   | 0.67 (0.25) | 0.47 (0.07) | 45.5 | 0.006 |

Values are expressed as the median and IQR (interquartile range). CST: Corticospinal tract. DTI values are expressed in $10^{-3}$ mm$^2$/s.
Supplementary Table 4: Univariate analysis between quantitative DTI-derived metrics and preoperative motor deficit.

| Variable                        | DTI metric | Preoperative deficit | Wilcoxon-Mann-Whitney Test |
|---------------------------------|------------|-----------------------|-----------------------------|
|                                 |            | No (n=7)              | Yes (n=4)                   | U   | Z     | P       | r   |
| Overall CST                     | FA         | 0.56 (0.03)           | 0.53 (0.01)               | 5   | 1.36  | 0.212   | 0.41|
|                                 | MD         | 0.92 (0.11)           | 0.88 (0.05)               | 13  | 0.29  | 0.833   | 0.09|
|                                 | AD         | 1.48 (0.12)           | 1.43 (0.07)               | 11  | 0.57  | 0.618   | 0.17|
|                                 | RD         | 0.64 (0.11)           | 0.6 (0.04)                | 12  | 0.29  | 0.830   | 0.09|
| Peritumoral CST region          | FA         | 0.64 (0.25)           | 0.34 (0.11)               | 3   | 2.08  | 0.042   | 0.63|
|                                 | MD         | 0.81 (0.27)           | 1.18 (0.23)               | 26  | 2.28  | 0.018   | 0.69|
|                                 | AD         | 1.43 (0.18)           | 1.62 (0.2)                | 23  | 1.7   | 0.109   | 0.51|
|                                 | RD         | 0.46 (0.36)           | 0.96 (0.42)               | 26  | 2.27  | 0.02    | 0.68|
| Ratio Ipsilateral/Contralateral | rFA        | 0.98 (0.04)           | 0.95 (0.06)               | 6   | 1.43  | 0.179   | 0.43|
| Overall CST                     | rMD        | 1 (0.04)              | 1.02 (0.09)               | 21  | 1.34  | 0.215   | 0.4 |
|                                 | rAD        | 1 (0.03)              | 1 (0.04)                  | 16  | 0.48  | 0.673   | 0.15|
|                                 | rRD        | 1 (0.09)              | 1.03 (0.15)               | 19  | 0.97  | 0.364   | 0.29|
| Ratio Ipsilateral/Contralateral | rFA        | 0.97 (0.07)           | 0.56 (0.33)               | 1   | 2.46  | 0.012   | 0.74|
| Peritumoral CST region          | rMD        | 1.08 (0.03)           | 1.6 (0.26)                | 26  | 2.27  | 0.024   | 0.68|
|                                 | rAD        | 1.06 (0.3)            | 1.21 (0.12)               | 19  | 0.95  | 0.412   | 0.28|
|                                 | rRD        | 1.16 (0.31)           | 2.44 (1.61)               | 28  | 2.65  | 0.006   | 0.8 |

Values are expressed as the median and IQR (interquartile range). CST: Corticospinal tract. DTI values are expressed in $10^{-3}$ mm$^2$/s.

Supplementary Table 5: Optimal cut-off based on DTI for permanent motor deficit.

| Variable                        | Cut-off | Sensitivity | Specificity | Optimal criterion | AUC  |
|---------------------------------|---------|-------------|-------------|-------------------|------|
| rFA Ipsilateral/Contralateral Peritumoral CST region | 0.8     | 1           | 0.875       | 0.875             | 0.917|

rFA: Fractional anisotropy ratio, AUC: Area under the curve