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Original Research

White Matter Integrity of the Corticospinal Tract for Estimation of Individual Patient Risk for Postoperative Neurological Deterioration after Glioma Surgery

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Abstract

Background: Tractography has become a standard tool for planning neurosurgical operations and has been proven to be useful for risk stratification. In various conditions, tractography-derived white matter integrity has been shown to be associated with neurological outcome. Postoperative performance has been shown to be a prognostic marker in glioma. We aimed to assess the relation of preoperative corticospinal tract (CST) integrity with postoperative neurological deterioration in patients with malignant glioma. **Methods**: We retrospectively analyzed a cohort of 24 right-handed patients (41.7% female) for perioperative neurological performance score (NPS) and applied our anatomical tractography workflow to extract the median fractional anisotropy (FA) of the CST in preoperative magnetic resonance imaging (MRI). **Results**: Median FA of the CST ipsilateral to the tumor correlated significantly with preoperative NPS ($p = 0.025$). After rank order correlation and multivariate linear regression, we found that the preoperative median FA of the right CST correlates with preoperative NPS, independently from epidemiological data ($p = 0.019$). In patients with lesions of the right hemisphere, median FA of the right CST was associated with a declining NPS in multivariate linear regression ($p = 0.024$). Receiver operating characteristic (ROC) analysis revealed an optimal FA cutoff at 0.3946 in this subgroup (area under the curve 0.83). Patients below that cutoff suffered from a decline in neurological performance significantly more often ($p = 0.020$). **Conclusions**: Assessment of preoperative white matter integrity may be a promising biomarker for risk estimation of patients undergoing craniotomy for resection of malignant glioma.

Keywords: corticospinal tract; DTI; glioma; MRI; neurological performance; tractography

1. Introduction

Tractography has become a widespread part of planning neurosurgical operations. In combination with other methods, it allows precise identification of white matter pathways and therefore enhances surgical performance and safety [1]. There is a rising number of studies investigating the correlation between diffusion tensor imaging (DTI)-derived parameters and neurological outcome [2–9].

The corticospinal tract (CST) is one of the most precisely described fiber bundles in the human brain. It comprises descending axons from the primary motor area in the precentral gyrus, as well as from the supplementary motor area and some parts of the parietal lobe. Together with a wider network of subcortical and cerebellar pathways it represents the anatomical basis for voluntary physical motion [10,11].

DTI measures the diffusivity along a number of axes in magnetic resonance imaging (MRI). Due to the diffusion barrier of their myelin sheaths, axons increase the directedness of diffusion, especially when a larger number of them crosses a voxel in the same direction. This directedness of diffusion correlates and is assessed with the fractional anisotropy (FA), which assumes values between 0 and 1, where higher values reflect a larger number of fibers sharing the same spatial orientation. A recent study of ours showed that most parts of the CST have FA values >0.15. Infiltrated and compressed CSTs have significantly lower FA values, so that the FA is among the markers for structural white matter integrity. FA values have been shown not to be normally distributed within the CST [12–15].

While the correlation of quantified white matter integrity and motor function recovery has been shown in patients with ischemic stroke, only little is known about its prognostic potential in neurosurgical patients who undergo surgery for malignant glioma. Current literature for this patient group comprises mostly measurements of distance between lesion and tract [16–18]. Neurological deterioration after glioma resection is a negative prognostic marker for overall survival [19]. Neurological performance depends on the integrity of several networks. However, the CST has the biggest volume and furthermore is a good candidate for automatic tractography applications in the future. Therefore, the aim of this study is to identify risk-factors for neurological deterioration, using quantified white matter integrity of the CST in preoperative MRI.

2. Materials and Methods

2.1 Patient Selection and Treatment

Data acquisition and analysis were approved by the local ethics committee (297/21-ek) and performed according to the data protection guidelines which included pseudonymization of personal data. We retrospectively searched the database of the University Hospital Leipzig for all patients with a malignant glioma (WHO grade 3 or 4), who underwent preoperative MRI between January 1, 2020 and March 31, 2021. Inclusion criteria were an MRI including DTI within 7 days before surgery and age of at least 18 years.

The criteria for DTI acquisition in clinical routine were guided by the interdisciplinary team and depended on eloquent location of the tumor, suspected histopathological malignancy, patient compliance, and eligibility for functional MRI or other complementing tools.

Clinical and histopathological data were obtained by reviewing the digital reports within our hospital. Neurological performance score (NPS) was assessed on the day before surgery as well as on the day of discharge after surgery within seven days. The NPS is a 5-point scale that quantifies the severity of neurological deficits, where "1" is no deficit, "2" is some deficit with adequate function for useful work, "3" is a moderate deficit that causes functional impairment, "4" is a major deficit causing disabilities like inability to move limbs, gross speech or visual disturbances, and "5" is the inability to make conscious responses [19,20].

Extent of resection (EOR) was assessed by an experienced neuroradiologist in postoperative MRI within 72 hours.

The dominant hemisphere was determined by assessment of handedness in every patient.

2.2 Image Acquisition

MRI was acquired within seven days before surgery on 3T Systems (Ingenia, Philips, Eindhoven, Netherlands and Prisma, Siemens, Erlangen, Germany) using a single-shot echo-planar imaging diffusion tensor imaging (DTI) sequences with equal settings (TR/TE = 7010/102 ms; FOV = 222 $\times$ 222 mm^2; matrix 112 $\times$ 112; 50 slices without gap; slice thickness 2.7 mm; 32 non-collinear directions, b-value = 1000 s/mm^2) and contrast-enhanced T1 weighted MPRAGE 3D dataset (TR/TE = 8.1/3.7 ms; FOV = 222 $\times$ 222 mm^2; matrix = 512 $\times$ 512; 170 slices without gap; slice thickness 1 mm) using a dedicated head coil.

2.3 Tractography

For tractography, the open-source software MRtrix3 (www.mrtrix.org) has been used [21]. The seed ROI (region of interest) was placed anterolaterally in the mesencephalon at the height of the cavernous sinus with a radius of 5 mm. The target ROI was placed between the anterior two-thirds of the internal capsule's posterior limb with a radius of 10 mm. The number of seeds was 106 in each hemisphere. The minimum streamline length was set to 30 mm, and the maximum streamline length was set to 250 mm. The FA cutoff was 0.15. The tractogram was examined by an experienced neurosurgeon and an experienced neuroradiologist. We excluded streamlines crossing to the contralateral hemisphere as well as collaterals to other fibre bundles and to the cerebellum. Then the FA values within the CST volumes were extracted.

Affection of the CST by the tumor was assessed by an experienced neuroradiologist. Unharmed and dislocated tracts were categorized as "unaffected". Compression was defined as a reduced CST volume due to dislocation in comparison to the contralateral hemishere. We defined contact of the CST to the tumor as infiltration. Compressed and infiltrated CSTs were categorized as "affected".

2.4 Statistical Analysis

Statistics were performed using SPSS Statistics 27 (IBM, Armonk, NY, USA) and in Python programming language using statistics modules [22–24]. Normality distribution was tested after D'Agostino-Pearson. For every CST, a median FA value was calculated and used for further statistical analysis. Perioperative change of the NPS (NPS$_Q$) was calculated as a quotient of postoperative NPS divided by preoperative NPS. We performed a nonparametric Spearman's rank correlation test to identify potentially significant results. Hereafter significant correlations underwent multivariate linear regression analysis including age, sex, extent of resection (EOR) and degree of malignancy. For variables with a significant correlation in multivariate analysis we performed a receiver-operator-characteristic (ROC) analysis to calculate a cutoff value. This cutoff was then used to dichotomize groups. Differences between dichotomized groups were analyzed with Mann-Whitney U test. Data is given as mean with standard error of the mean (SEM) if not stated otherwise. p-values < 0.05 were considered statistically significant.

3. Results

3.1 Patients

We identified 28 patients with malignant glioma who had received an MRI with DTI sequence within seven days before neurosurgery. Left-handed patients had been excluded due to their small sample size (n = 3). One patient had a tumor affecting both hemispheres equally and therefore couldn't be categorized by lesion's side and was not included into analysis. 24 patients were analyzed.

Average age at time of surgery was 58.1 ± 3.4 years with 41.7% female patients. No severe postoperative complication like spontaneous hemorrhage, ischemic stroke, or encephalitis occurred within the cohort. 8 patients (33.3%) showed a constant or improved neurological performance within the first seven days. Mean NPS was 2.3 ± 0.1 before surgery, and 2.6 ± 0.2 at discharge after surgery. Median FA in all CSTs was 0.37 ± 0.02. Epidemiological and clinical data are given in Table 1. Example tractograms are shown in Fig. 1.

Table 1. Baseline characteristics.

Variable	Value
Patients	24
Age [years]	58.1 ± 3.4
Female	41.7%
Affected hemisphere L/R	11/13
IDH-wildtype glioblastoma	17 (71%)
Astrocytoma WHO grade 4	2 (8%)
Astrocytoma WHO grade 3	4 (17%)
Oligodendroglioma WHO grade 3	1 (4%)
CST affected/unaffected	11/13
NPS preoperative	2.3 ± 0.1
- for affected hemisphere L/R	2.3 ± 0.2/2.4 ± 0.2
NPS postoperative	2.6 ± 0.2
- for affected hemisphere L/R	2.6 ± 0.3/2.6 ± 0.3
NPS_Q (NPS postoperative/preoperative)	1.18 ± 0.12
- for affected hemisphere L/R	1.26 ± 0.22/1.12 ± 0.13
Median FA left CST	0.38 ± 0.01
Median FA right CST	0.36 ± 0.02
EOR (gross total/subtotal/biopsy)	11/12/1
- for tumors of the left hemisphere	7/4/0
- for tumors of the right hemisphere	4/8/1

IDH, isocitrate dehydrogenase; WHO, world health organization; CST, corticospinal tract; NPS, neurological performance score; EOR, extent of resection.

3.2 Rank Order Correlation

CST affection significantly correlated with median FA (r = –0.41, p = 0.050).

Median FA of the CST ipsilateral to the tumor correlated significantly with preoperative NPS (r = –0.46, p = 0.025). Dichotomized by affected hemisphere, the only significant correlation was between median FA of the right CST and NPS_Q in patients with lesions of the right hemisphere (r = 0.66, p = 0.013). These correlations were further analyzed in multivariate analysis. Other correlations were not statistically significant.

3.3 Multivariate Analysis

In multivariate regression analysis, preoperative median FA of the right CST showed a slightly non-significant correlation with preoperative NPS (p = 0.052). In subgroup analysis of patients with lesions of the right hemisphere preoperative median FA of the right CST showed a significant correlation with NPS_Q in multivariate regression analysis (p = 0.024). This was independent from epidemiological data (Table 2).

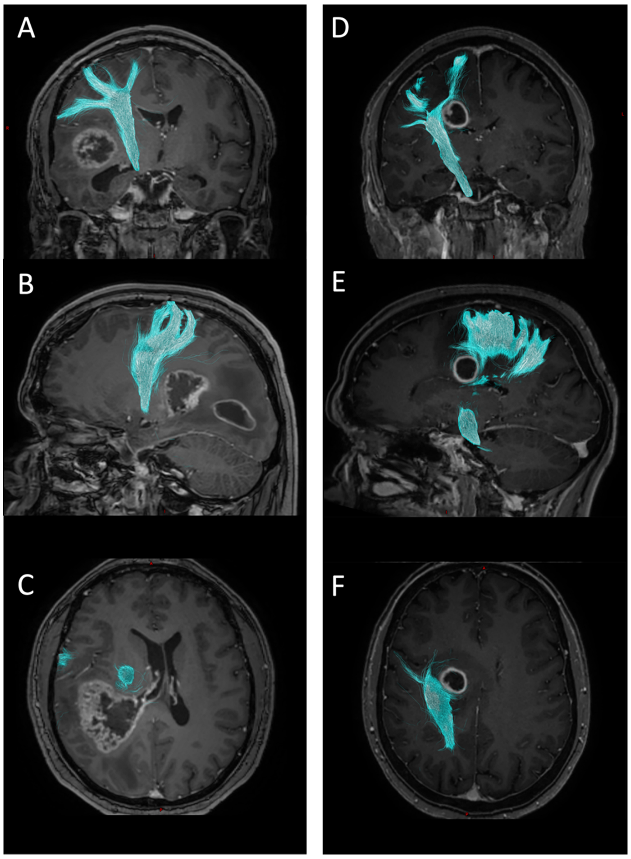

Fig. 1. Example tractograms of the right CST (cyan). Preoperative contrast-enhanced T1-weighted MPRAGE sequence. (A–C) 34-year-old male patient with multifocal glioblastoma WHO grade 4 in the right hemisphere. NPS preoperative 2, postoperative 4. Preoperative median FA of the right CST 0.3972. (D–F) 62-year-old female patient with glioblastoma WHO grade 4 in the right hemisphere. NPS preoperative 2, postoperative 1. Preoperative median FA of the right CST 0.2706.

3.4 ROC Analysis

ROC analysis failed for the correlation of preoperative NPS and median FA of the right CST, so that a significant cutoff for dichotomization of the whole cohort could not be calculated.

In ROC analysis for identification of patients with postoperative decline in neurological performance (NPS_Q >1) by median FA of the right CST, the optimal cutoff was 0.3946 with an area under the curve of 0.83 (sensitivity 75.0%, specificity 88.9%, Youden index 0.639). Patients with lesions of the right hemisphere above that cutoff suffered from neurological decline significantly more often

Table 2. Multivariate regression analysis for association with NPS_Q.

Affected Hemisphere	Variable	Value	p-value (NPS_Q)
left (n = 11)	age	62.3 ± 5.3	0.345
	sex	36.4% female	0.847
	grade of malignancy	3.8 ± 0.2	0.590
	preoperative median FA left CST	0.35 ± 0.03	0.069
	preoperative median FA right CST	0.40 ± 0.02	0.197
	extent of resection (EOR)	7/4/0 (gross total/subtotal/biopsy)	*0.028**
right (n = 13)	age	54.5 ± 4.2	0.211
	sex	46.2% female	*0.044**
	grade of malignancy	3.7 ± 0.1	0.915
	preoperative median FA left CST	0.41 ± 0.01	0.592
	preoperative median FA right CST	0.33 ± 0.02	*0.024**
	extent of resection (EOR)	4/8/1 (gross total/subtotal/biopsy)	0.547

Statistically significant results are marked with an asterisk and written in italics. NPS, neurological performance score; NPS_Q, NPS (postoperative)/NPS (preoperative); FA, fractional anisotropy; CST, corticospinal tract; *, $p < 0.05$.

(NPS_Q 0.90 ± 0.08 versus 1.63 ± 0.24, $p = 0.020$).

3.5 Sub-Group Comparison

Mann-Whitney U test revealed no significant difference in NPS_Q between men and women with lesions in the right hemisphere. However, men suffered from a declining neurological performance more often after surgery in this subgroup (1.36 ± 0.18 versus 0.85 ± 0.11, $p = 0.073$).

Concerning epidemiological data in patients with tumors of the left or the right hemisphere, we found no significant differences for age (p = 0.207), sex (p = 0.691), grade of malignancy (p = 0.865), or extent of resection (p = 0.150).

In contrast, for patients with tumors of the dominant left hemisphere, gross total resection was associated with less neurological deterioration (NPS_Q 0.93 ± 0.13 versus 1.83 ± 0.44, $p = 0.047$).

4. Discussion

Correlation of white matter integrity with neurological recovery has been shown in patients with ischemic stroke [4,8,9]. In neurosurgery, tractography is already being used for preoperative risk stratification by measuring tract-to-fiber-distance [7,25]. Considering it is a well-known biomarker for white matter integrity, we decided to measure fractional anisotropy (FA) [26]. We described before that FA values of the CST are not normally distributed, and therefore analyzed median values [15]. Because neurological performance may have been influenced by patient characteristics like age, sex, extent of resection and the grade of malignancy, we performed multivariate analyses to correct for epidemiological data. To clarify which variables should be implemented in multivariate linear regression, we first performed bivariate Spearman correlation and analyzed significant results further.

While gross total resection of tumors of the dominant left hemisphere was associated with less neurological deterioration, this effect was not statistically significant for tumors of the non-dominant right hemisphere. This may be the result of decompression of the dominant left hemisphere. Also, this effect may have obscured a significant correlation of preoperative median FA with NPS_Q, which could potentially have been observed in a larger sample size.

Importantly, preoperative NPS correlated with preoperative median FA of the right CST, where a higher FA value marked better neurological performance. For patients with tumors of the non-dominant right hemisphere, preoperative median FA of the right CST correlated with a decline of NPS after surgery independently of age, sex, extent of resection and WHO grade. Since only right-handed patients had been analyzed in this study, these lesions were all located in the non-dominant hemisphere. Moreover, the FA cutoff at 0.3946 dichotomized these patients with a significant difference in neurological deterioration. Hence, an estimation of individual patient risk for a decline in neurological performance could be applied. Surprisingly, white matter integrity in the non-dominant hemisphere appeared to predict neurological decline when a lesion was present on this side. Higher white matter integrity of the non-dominant right CST was even associated with a higher incidence of neurological decline, while at the same time it was associated with better preoerative neurological performance.

There are several possible explanations for these findings. First, a lowered FA might be a sign of impending or proceeding neuroplasticity effects, protecting patients from further neurological damage [18]. Also, plasticity might be triggered by white matter damage to the CST and actually manifest elsewhere [27].

However, we only acquired MR images at a single point in time. Therefore our data cannot elaborate on microstructural changes due to craniotomy and tumor resection, nor due to tumor growth.

Second, surgical strategy in the non-dominant right hemisphere might have been different from the contralateral side. There were fewer gross total resections in the non-dominant right hemisphere, but EOR correlated with NPS_Q only for tumors of the dominant left hemisphere. Also, patients with lesions of the non-dominant right hemisphere showed less decrease in neurological performance. Therefore, our retrospective risk stratification in this subgroup is unlikely to be coincidental or due to surgical strategy.

It is further possible, that FA in the CST is mainly linked to neurological performance at the time of imaging. It would stand to reason that these patients are more likely to decline than those who already suffered neurological damage before surgery.

Since the NPS includes functions of movement, speech and vision, this may be a sign of the non-dominant hemisphere taking part in higher neurological functions. Therefore, the CST may be a part of functional networks exceeding voluntary physical motion, or its integrity might represent a marker for the risk of surgical damage to adjacent functional networks in the non-dominant right hemisphere.

Overall, white matter integrity of the CST alone cannot predict neurological performance in detail. Especially CST integrity of the dominant left hemisphere yielded no statistically significant results. Although this may be different in future studies with larger sample sizes, our results show that also lesions in the non-dominant right hemisphere must trigger vigilance for preventing neurological decline, especially when CST integrity appears high.

Limitations

Due to the retrospective nature of the here-presented study, an investigator bias in the assessment of neurological performance cannot be fully ruled out. Also, the consideration of parallel and radial diffusivity as surrogate markers for the differentiation between axonal and myelination damage, respectively, may have shown additional, significant effects on a smaller scale [28].

Intraoperative identification of the CST with direct eletrical stimulation was not applied. The tractography workflow relied on anatomical identification of landmarks instead of techniques such as functional MRI or transcranial magnetic stimulation. However, recent data showed that the anatomical approach is in fact not inferior to functional identification of regions of interest (ROIs) [29]. Also, ROI placement in our workflow aimed at assessing the subcortical volume of the CST in its section between decussation and cortex. This has to be kept in mind when interpreting results from other groups with different workflows.

It should also be noted that other epidemiological factors, apart from those assessed in our study, could potentially influence neurological deterioration as a measured outcome. It is especially possible that other fiber bundles, for example in the language network, may be associated with neurological outcome [30].

Finally, our cohort comprises patients with different histopathological entities in different locations which may affect white matter integrity and subcortical pathways differently. We addressed this issue by applying multivariate analyses. However, future studies should be prospective and multicentric to compare patients with histopathologically different lesions stratified by their respective locations.

5. Conclusions

Preoperative median FA of the corticospinal tract ipsilateral to the tumor correlates with preoperative neurological performance. Higher preoperative FA of the corticospinal tract in the non-dominant right hemisphere may be a prognostic marker for decline of neurological performance after resection of malignant gliomas in that hemisphere. Prospective multicentric studies are needed to verify the results and should also take into account white matter integrity of other tracts, as well as potentially divergent impacts of specific tumor entities in different locations.

Author Contributions

TW and GP designed the research study. AH, TW and GP performed the research. MKF, CSa, JK, HJM, FA, CSch, JM and KTH provided resources in clinical assessment, imaging, and infrastructure. TW, AH and GP analyzed the data. TW, AH and GP wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The data acquisition and analysis was approved by the ethics committee of Leipzig University (297/21-ek) and performed according to the data protection guidelines which included the pseudonymization of personal data.

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Conflict of Interest

The authors declare no conflict of interest.

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