Intraoperative Visualization of Fiber Tracking Based Reconstruction of Language Pathways in Glioma Surgery

Daniela Kuhnt, MD*
Miriam H. A. Bauer, MSc*
Andreas Becker, MD*
Dorit Merhof, PhD§
Amir Zolal, MD||
Mirco Richter, MSc§
Peter Grummich, PhD‡
Oliver Ganslandt, MD, PhD‡
Michael Buchfelder, MD, PhD‡
Christopher Nimsky, MD, PhD*

*Department of Neurosurgery, University of Marburg, Marburg, Germany; ‡Department of Neurosurgery, University of Erlangen-Nuremberg, Erlangen, Germany; §Visual Computing, University of Konstanz, Konstanz, Germany; ||Department of Neurosurgery, J.E. Purkinje University, Usti nad Labem, Czech Republic

Correspondence:
Daniela Kuhnt, MD,
Department of Neurosurgery,
University of Marburg, Baldingerstrasse,
35043 Marburg, Germany.
E-mail: kuhntd@med.uni-marburg.de

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BACKGROUND: For neuroepithelial tumors, the surgical goal is maximum resection with preservation of neurological function. This is contributed to by intraoperative magnetic resonance imaging (iMRI) combined with multimodal navigation.

OBJECTIVE: We evaluated the contribution of diffusion tensor imaging (DTI)-based fiber tracking of language pathways with 2 different algorithms (tensor deflection, connectivity analysis [CA]) integrated in the navigation on the surgical outcome.

METHODS: We evaluated 32 patients with neuroepithelial tumors who underwent surgery with DTI-based fiber tracking of language pathways integrated in neuronavigation. The tensor deflection algorithm was routinely used and its results intraoperatively displayed in all cases. The CA algorithm was furthermore evaluated in 23 cases. Volumetric assessment was performed in pre- and intraoperative MR images. To evaluate the benefit of fiber tractography, language deficits were evaluated pre- and postoperatively and compared with the volumetric analysis.

RESULTS: Final gross-total resection was performed in 40.6% of patients. Absolute tumor volume was reduced from 55.33 ± 63.77 cm^3 to 20.61 ± 21.67 cm^3 in first iMRI resection control, to finally 11.56 ± 21.92 cm^3 ($P < .01$). Fiber tracking of the 2 algorithms showed a deviation of the displayed 3D objects by <5 mm. In long-term follow-up only 1 patient (3.1%) had a persistent language deficit.

CONCLUSION: Intraoperative visualization of language-related cortical areas and the connecting pathways with DTI-based fiber tracking can be successfully performed and integrated in the navigation system. In a setting of intraoperative high-field MRI this contributes to maximum tumor resection with low postoperative morbidity.

KEY WORDS: Diffusion tensor imaging, Glioma, Language pathways

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Language processing is a complex process, and the network of language-related pathways is still not completely understood. Lesions of the arcuate fasciculus (AF), which was first described in 1822 by Burdach[1] as a system of fibers surrounding the Sylvian fissure, result in the disconnection syndrome conduction aphasia. Today, we know that conduction aphasias form a heterogeneous group with various clinical symptoms. Thus, the detailed anatomy of the AF and the associated cortical areas are still under intense investigation. Catani and Ffytche[2] published a model of the AF in 2005. This model displayed the AF consisting of a direct segment and an indirect pathway. To date, several authors have postulated the extension of language fibers beyond the classical cortical areas, including the middle frontal gyrus, the precentral gyrus, and the posterior middle temporal gyrus.[2,3] Considering 2 major language components, phonology and lexical semantics, fibers for phonologic processing are included in the superior longitudinal fasciculus, connecting frontal gyri with the superior temporal gyrus, the planum temporale,[4] and the supramarginal gyrus.[5] The lexical-semantic

ABBREVIATIONS: AF, arcuate fasciculus; **CA,** connectivity analysis; **DTI,** diffusion tensor imaging; **EOR,** extent of resection; **FA,** fractional anisotropy; **fMRI,** functional magnetic resonance imaging; **GTR,** gross total resection; **iMRI,** intraoperative magnetic resonance imaging; **IOFF,** inferior occipitofrontal fascicle; **WHO,** World Health Organization system is thought to be part of the inferior occipitofrontal fascicle (IOFF), initially described by Kier et al.[6]

On the basis of the findings of Basser et al,[7] diffusion tensor imaging (DTI)-based fiber tractography became a noninvasive method to estimate the position and course of white matter tracts and their extent in vivo. Various algorithms have been established for reconstruction of major white matter tracts, which are separated in deterministic and probabilistic tracking methods. To facilitate and improve reconstruction, many approaches try to optimize tracking of white matter bundles by using advanced magnetic resonance (MR) sequences or by establishing different algorithms. The concept of connectivity analysis (CA) seems to be a promising approach. In addition to anatomical image data, information on functional brain areas as given by functional magnetic resonance imaging (fMRI) or DTI fiber tractography can be displayed in navigation systems. A combined use of functional navigation and intraoperative MRI (iMRI) allows maximum resection while preserving neurological function.[8,9] Maximum resection with minimum postoperative morbidity has lately been accepted as the surgical concept for neuroepithelial tumors.[10] In this way, the influence of DTI-based fiber tractography for language pathways and intraoperative high-field MRI is evaluated for a cohort of patients with gliomas located in the vicinity of language-related structures.

OBJECTIVE

We present 32 patients with neuroepithelial tumors, adjacent to language-related areas, for whom cortical language sites and the connecting pathways were successfully visualized in the surgical field. DTI-based fiber tracking was performed with 2 different algorithms (tensor deflection and CA algorithm).[11] Furthermore, the integrity of cortical areas and fibers was assessed clinically, obtaining language deficits pre- and postoperatively and compared with the extent of resection (EOR).

The aim is to show that DTI based fiber tractography for language pathways can be successfully integrated into the navigation system and whether the setting of intraoperative 1.5T MRI is associated with a low postoperative morbidity in combination with maximum tumor resection.

PATIENTS AND METHODS

Patient Collective

From 2003 to 2008 we investigated a collective of 32 patients (15 male and 17 female) with neuroepithelial tumors, classified according to the World Health Organization (WHO) in the Department of Neurosurgery, University Erlangen-Nuremberg, Germany (Table 1). There was recurrent tumor in 4 cases. Mean patient age was 47.19 ± 13.07 (range, 24-68) years. In all cases, neuronavigation was used intraoperatively, displaying the integrated language-related cortical areas and the connecting fiber bundles. The patients were selected prospectively according to the following criteria:

TABLE 1. Types of Neuroepithelial Lesions

Lesion	No. of Patients
Astrocytoma (II)	1
Oligodendroglioma (II)	1
Oligoastrocytoma (II)	3
Ganglioglioma (I)	2
Anaplastic astrocytoma (III)	4
Anaplastic oligoastrocytoma (III)	4
Anaplastic oligodendroglioma (III)	4
Glioblastoma multiforme (IV)	13
Total	32

- radiologically neuroepithelial tumor
- tumor located on the language-dominant hemisphere according to functional MRI (fMRI)
- tumor in less than 20 mm distance to language-related structures (based on experiences with DTI tractography of the pyramidal tract[12])

In 30 patients, lesions were located on the left side, whereas 2 patients had lesions located in the right hemisphere. These 2 patients were left handed; the other patients were right handed. Preoperatively, the dominant hemisphere was detected with fMRI in all cases.

Informed consent for the performance of iMRI and acquisition of fMRI was obtained from all patients or adequate family members preoperatively.

For assessment of language deficits, the National Institutes of Health Stroke Scale was used (item 9: best language: 0 = normal, 1 = mild to moderate aphasia, 2 = severe aphasia, 3 = global aphasia), which has been applied on glioma patients in other studies.[13] For comparison of pre-, and postoperative language deficits the patient collective was grouped as follows: group A, no postoperative aggravation of language deficits; group B, mild postoperative language impairment, then back to baseline function at discharge; group C, postoperative language deterioration, improved until discharge; group D, postoperative language impairment without improvement until discharge.

Functional MRI

For localization of Broca's and Wernicke's area, fMRI data sets were obtained preoperatively using echo planar imaging sequences with 25 slices, slice thickness of 3 mm, and TR/TE of 2470/60 ms. A box car paradigm with visual stimulations was used with 30 stimulations in activity and 30 stimulations in recovery. Motion correction was performed with image-based prospective acquisition correction.[14] Activation maps were constructed by analyzing the correlation between activation maps and square wave reference function for each pixel. Pixels exceeding a significance threshold (>0.3, $P < .001$) were displayed if at least 6 contiguous voxels built a cluster. After statistical analysis of the resulting data sets with the Brain Voyager Software (Brain Innovation B.V., Maastricht, Netherlands) the resulting activity fMRI maps was saved as Digital Imaging and Communications in Medicine data for integration into the navigation system. The activity clusters were used as seed regions for the reconstruction of language-associated fiber tracts.

Diffusion MRI and Fiber Tracking

DTI-based fiber tracking was performed on the base of a single-shot spin-echo diffusion-weighted sequence data set (echo planar imaging readout, TR/TE 9200/86 ms, matrix size 128 × 128, field of view 240 mm, slice thickness 1.9 mm, b value 0 and 1000 s/mm^2, respectively, 6 diffusion gradient directions). Two different tracking algorithms were used: tensor deflection and CA. Tensor deflection, first described by Lazar et al,[15] is integrated in the iPlan Cranial 2.5 software (BrainLab, Feldkirchen, Germany) and was used in all cases. CA is a probabilistic approach, based on the principle of path finding. The anatomical T1 MR data sets were rigidly registered with the DTI b0 images and the fMRI maps.[16]

Reconstruction and Integration Into Neuronavigation System

The results of the fMRI analysis were rigidly registered with the anatomical data sets. A first volume of interest is placed in the region of temporoparietal activation, and the algorithm is started. To restrict the resulting fiber set to language-related fibers, a second volume of interest (region of frontal activation) is used as an include region. Reconstruction with CA algorithm was realized within the medical imaging platform MedAlyVis (Medical Analysis and Visualization).[11] Rigid registration of DTI b0 images and fMRI activation maps was performed, followed by region of interest placement according to activation zones and search space adaption to structure of interest. After 3D hull generation covering reconstructed fibers, results were transferred to iPlan Cranial 2.5 for final segmentation via thresholding.

iMRI and Assessment of Tumor Volume

iMRI was performed in all cases on a 1.5 T MR (Siemens Sonata, Siemens, Erlangen, Germany).[8] The first iMRI, including 1.0 mm isotropic 3D magnetization prepared rapid gradient echo, was obtained immediately before skin incision, with the patient's head already fixed for registration. These image data were fused with the MR images (identical sequences, contrast-enhanced) that had been acquired at least 1 day before surgery on the same scanner, whereby tumor segmentation had been performed on these scans. The further intraoperative scans for resection control were performed each after the surgeon's estimation of best possible tumor resection. Tumor segmentation and postoperative analysis was performed with the Vector Vision planning software.[8]

Statistics

All tumor volumes are presented in mean ± standard deviation (SD). Statistical analysis was performed in PASW Statistics 18 for Mac (SPSS Inc., Chicago, Illinois).

The Wilcoxon (Mann-Whitney *U*) Test was used for determining the influence of iMRI on EOR (residual tumor volume in first iMRI vs residual tumor volume in final iMRI).

For analysis of neurological deficits in the groups "further tumor resection after iMRI" vs "no further tumor resection after iMRI," a linear regression model was used.

A P value of $<.05$ was considered as significant.

RESULTS

In all 32 cases, cortical language sites as well as the connecting white matter tracts were visualized with the tensor deflection algorithm of iPlan Cranial 2.5 for DTI-based fiber tracking (fractional anisotropy [FA]) value: 0.3) (Figure 1). Furthermore, reconstruction using the CA algorithm was obtained in the latter 23 cases (FA value: 0.3). These data were successfully transferred into iPlan Cranial 2.5 in 5 cases because of the time-consuming process. In these cases, visualized data of both methods were displayed within the same image (Figure 2). A comparison of the 2 algorithms alongside the intraoperative setting was performed in all cases. Although the fiber bundles were not fully congruent in form and size, there was a mean deviance of approximately 5 mm in the central part of the created 3D objects. Only for Near-cortical parts of the reconstructed tract, showed a deviation up to 10 to 15 mm (Figure 2). The fiber-tracking procedure lasted 5 to 10 minutes for the tensor deflection algorithm and 20 to 30 minutes for the CA algorithm. The image distortion of the b0 images impeded registration with less than 2 mm in the areas of interest.

All data were successfully displayed in the microscope field of view intraoperatively (Figure 3). Navigation accuracy documented

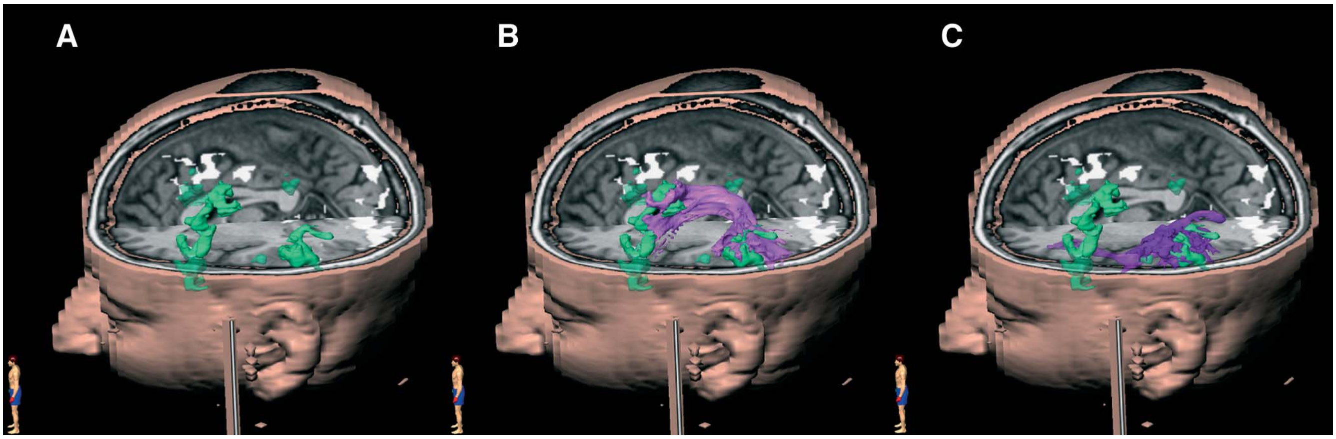

FIGURE 1. *Clinical case.* **A**, *Broca and Wernicke area visualized with fMRI (green).* **B**, *DTI-based fiber tracking (tensor deflection) showing the arcuate fasciculus (light purple).* **C**, *DTI-based fiber tracking (tensor deflection) showing the occipitofrontal inferior tract (dark purple). fMRI, functional MRI; DTI, diffusion tensor imaging.*

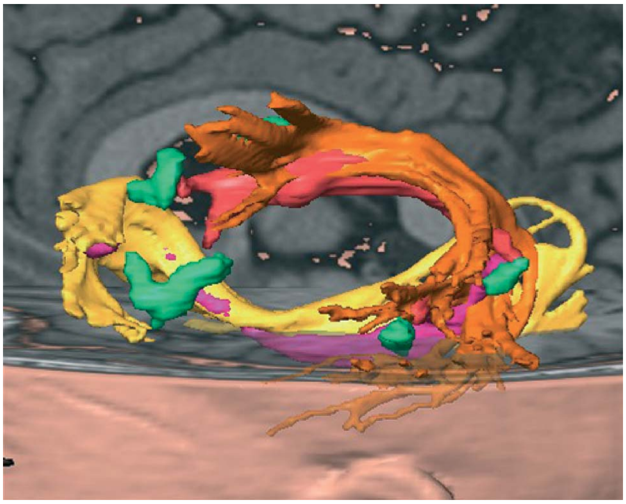

FIGURE 2. *Comparison between tensor deflection algorithm (AF, orange; IOFF, yellow) and connectivity analysis algorithm (AF, red; IOFF, purple), Broca and Wernicke areas segmented in green according to fMRI. fMRI, functional MRI; AF, arcuate fasciculus; IOFF, inferior occipitofrontal fascicle.*

as target registration error was 0.4 to 3.0 (1.69 ± 0.62) mm, measuring the offset of an additional skin fiducial marker attached on the patient's head not used for registration.

Tables 2 and 3 summarize the patient collective, the surgical procedures with the resected tumor volume, and the postoperative deficits. In 10 cases (31.25%), surgery was continued after iMRI, which revealed residual tumor. The mean preoperative tumor volume was 55.33 ± 63.77 cm^3, in first iMRI resection control it was 20.61 ± 21.67 cm^3, and in final iMRI it was 11.56 ± 21.92 cm^3. Thus, EOR was significantly reduced owing to iMRI and continued surgery ($P < .001$). Gross total resection was finally achieved in 13 patients (40.63%), in 2 cases because of iMRI.

Language deficits were obtained pre- and postoperatively (at discharge) for all patients according to the National Institutes of Health Stroke Scale. Nineteen patients did not show any language deficits preoperatively, 8 patients had "mild to moderate" aphasia, and 5 patients had "severe" aphasia. No patient had global aphasia preoperatively. In 23 patients, there was no postoperative language impairment (71.88%) (group A). Nine patients (28.13%) showed a deterioration of language deficits postoperatively. In 6 cases (18.75%), there was a complete remission of these deficits until discharge (group B). We observed a language impairment, which only partially resolved in 3 patients until discharge (9.38%) (group C). Long-term follow-up after 4 months showed persistent aphasia in only 1 patient (3.1%).

Group A included 8 patients with 100% tumor volume EOR, 2 patients with 99.9% to 98% EOR, 0 patients with 97.9% to 95% EOR, 3 patients with 94.9% to 90% EOR, and 10 patients with <90% EOR (Table 4). Group B included 3 patients with 100% tumor volume EOR, 0 patients with 99.9% to 98% EOR, 0 patients with 97.9% to 95% EOR, 0 patients with 94.9% to 90% EOR, and 3 patients with <90% EOR. Group C included 2 patients with 100% tumor volume EOR, 0 patients with 99.9% to 98% EOR, 0 patients with 97.9% to 95% EOR, 1 patient with 94.9% to 90% EOR, and 0 patients with < 90% EOR. Comparing the postoperative language deficits of the group "further tumor resection after iMRI" with the group "no further resection after iMRI" at the time of discharge, there was no significant difference according to linear regression ($P = .672$).

Illustrative Case (Figure 4)

A 36-year-old patient presented after 1 episode of speech arrest as well as, most likely, focal motor seizure of the tongue. The MRI scan revealed a partially cystic lesion in the right frontal lobe. fMRI detected cortical language sites bilaterally. Tumor resection was performed with iMRI guidance and intraoperative visualization of the cortical language sites and connecting pathways. iMRI secured a complete tumor removal. Postoperatively, there was a paresis of

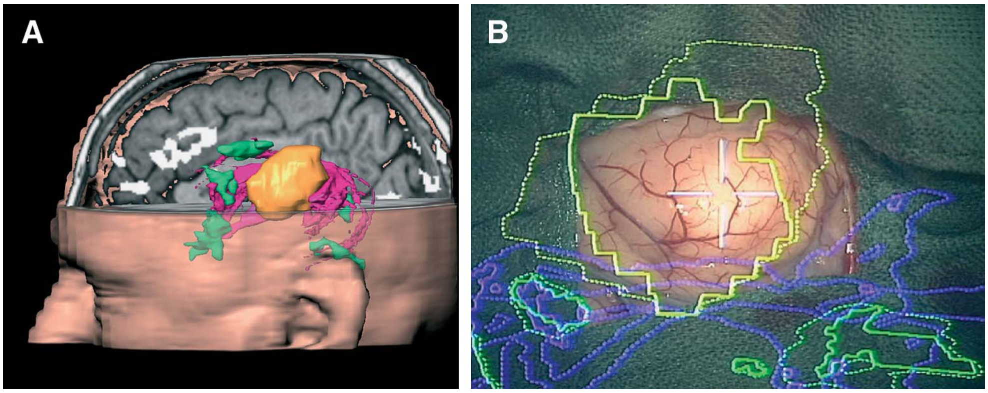

FIGURE 3. **A**, *navigation screenshot—sagittal view. Fiber tracking with CA algorithm (tumor, yellow; green, Broca and Wernicke area; pink, language pathways).* **B**, *microscope view intraoperatively (same colors). CA, connectivity analysis.*

TABLE 2. Patient Cohort: Localization, WHO Grade/Lesion Type, Pre-/Intra-/Postoperative Tumor Volume and Tumor Volume Reduction[a]

			Tumor Volume, mL				
Patient No.	WHO Grade Lesion	Localization	Pre-OP	I-OP	Post-OP	Red, %	Group[b]
1	IV	Temporal	15.20		10.05	33.9	A
2	I	Temporal	5.97		0.00	100.0	A
3	IV	Frontal	75.97		0.00	100.0	A
4	IV	Frontotemporal	38.57		5.21	86.5	A
5	III	Frontal	32.10	0.71	0.23	99.3	A
6	II	Frontal	43.09	3.08	0.59	98.3	A
7	III	Frontal	34.30		2.88	91.6	A
8	IV	Temporal	44.49		0.00	100.0	B
9	IV	Temporal	72.75		4.86	72.6	A
10	III	Frontal	37.91		0.00	100.0	A
11	II	Temporal	31.82	21.44	4.75	85.1	A
12	III	Temporal	14.92		0.00	100.0	A
13	III	Frontal	14.92		0.00	100.0	A
14	III	Temporal	55.5	3.31	0.00	100.0	C
15	II	Frontal	10.21	2.08	0.00	100.0	A
16	IV	Temporo-occipital	160.93	34.99	31.14	80.7	A
17	III	Temporal	31.38	3.08	2.79	91.1	A
18	III	Frontal	16.98		0.00	100.0	A
19	III	Temporal	30.50		2.4	92.1	C
20	II	Frontal	86.04		23.29	72.9	B
21	IV	Frontal	16.80		7.07	57.9	A
22	III	Frontal	73.54		52.47	28.7	A
23	IV	Temporal	101.88	39.91	15.28	85.0	A
24	III	Frontal	13.39		0.00	100.0	B
25	IV	Temporal	99.74	63.04	53.75	46.1	A
26	III	Frontal	44.90		23.18	48.4	A
27	I	Temporal	1.68		0.00	100.0	A
28	II	Temporoparietal	47.73	34.47	15.79	66.9	B
29	IV	Frontotemporal	116.77		103.03	11.8	A
30	IV	Parietal	44.79		0.00	100.0	B
31	IV	Temporo-occipital	24.42		11.27	53.9	B
32	IV	Temporal	25.57		0.00	100.0	C

[a]WHO, World Health Organization; Pre-OP, preoperative; I-OP, intraoperative; Post-OP, postoperative; Red, reduction.
[b]Group A, no postoperative aggravation of language deficits; group B, mild postoperative language deterioration then back to baseline function at discharge; group C, postoperative language deterioration, improved until discharge; group D, postoperative language deterioration without improvement until discharge.

the facial nerve House-Brackmann grade II as well as a slight dysarthric disorder. These deficits almost completely resolved by discharge. After 1 year, there was a complete remission. The neuropathological evaluation revealed an anaplastic astrocytoma (WHO grade III), so the patient received additional stereotactic radiation.

DISCUSSION

Visualization of language-related cortical areas and the connecting white matter bundles within the microscope heads up display and intraoperative update of the anatomic image data after iMRI contributes to maximum EOR with minimum postoperative morbidity. This concept is now widely accepted in glioma surgery, because common literature considers maximum EOR as a positive predictive value for longer survival in low- and high-grade gliomas.[10] The application of 2 different algorithms for DTI-based fiber tracking combined with the clinical outcome corroborates the utility of the procedure.

Intraoperative MRI With Multimodal Navigation and Clinical Outcome

A combination of intraoperative MRI and multimodal navigation unites the advantages of intraoperative resection control, compensation for brain shift, and preservation of neurological function by displaying white matter tracts intraoperatively.[17] The intraoperative update was performed by rigid registration of pre- and intraoperative image data.[18]

Several studies found that subcortical stimulation methods contribute to maximum safe resection in glioma surgery for lesions near the pyramidal tract, but also for language pathways.[19,20] Our results of postoperative morbidity regarding language deficits are

TABLE 3. Patient Cohort: Pre- and Postoperative Deficits and Classification According to Deficit Groups

Patient No.	Preoperative Deficits	Postoperative Deficits	Group[a]
1	None	None	A
2	None	None	A
3	None	None	A
4	Mild sensomotor aphasia	Status idem	A
5	Motor aphasia	Status idem	A
6	None	None	A
7	None	None	A
8	Mild motor aphasia	Mild deterioration, then back to status idem	B
9	None	None	A
10	None	None	A
11	Mild motor aphasia	Status idem	A
12	None	None	A
13	None	None	A
14	Mild motor aphasia	Motor aphasia, then better	C
15	None	None	A
16	None	None	A
17	None	None	A
18	None	None	A
19	Motor aphasia	Deterioration, then better	C
20	Mild motor aphasia	Mild deterioration, then back to status idem	B
21	Motor aphasia	Status idem	A
22	None	None	A
23	None	None	A
24	Mild motor aphasia	Mild deterioration, then better	B
25	None	None	A
26	None	None	A
27	None	None	A
28	Mild sensomotor aphasia	Deterioration, then better	B
29	None	None	A
30	Sensor aphasia	Deterioration, then back to status idem	B
31	Motor aphasia	Deterioration, then back to status idem	B
32	Mild motor aphasia	Deterioration, then better	C

[a]Group A, no postoperative aggravation of language deficits; group B, mild postoperative language deterioration then back to baseline function at discharge; group C, postoperative language deterioration, improved until discharge; group D, postoperative language deterioration without improvement until discharge.

similar to the ones presented in these publications, evaluating the postoperative morbidity for lesions in the proximity of language-related structures, using intraoperative electrophysiological mapping for detection of language pathways. Bello et al[20] presented a study of 88 gliomas; a permanent deficit occurred in 2.3% of all cases. Sanai et al[21] published a series of 250 patients in 2008, including intraoperative language mapping. Six months after surgery, only 1.6% of patients had a persisting language deficit. Furthermore, it has been shown that a combination of DTI-based fiber tracking and intraoperative subcortical stimulation enhances the surgical performance for lesions near language pathways and the corticospinal tract.[22-25] Regarding intraoperative electrostimulation together with iMRI, Hatiboglu et al[26] recently showed that intraoperative cortical mapping can be successfully used in a high-field MRI environment. As opposed to these studies, McGirt et al[27] presented a retrospective study of 306 patients with glioblastoma multiforme with postoperative language deficits in 15%. In this study, no fiber tracking or electrophysiology was obtained intraoperatively.

Other studies evaluated the influence of iMRI resection control on EOR in glioma surgery, including a volumetric analysis of tumor volume, which also showed similar results for EOR and the influence of iMRI. Intraoperative low-field MRI was used by Busse et al,[28] Bohinski et al,[29] and Schneider et al.[30] Busse et al[28] reported gross-total glioma resection in 22.7%. Bohinski et al[29] reported that gross total resection (GTR) was enhanced from 47% to 72.5% after iMRI and continued surgery. The surgical goal was initially achieved in only 47%. Schneider et al[30] evaluated a cohort of 31 patients with glioblastoma multiforme. GTR was enhanced from 2 to 11 patients (36%) after iMRI and continued surgery; residual tumor was found in the first iMRI in 93.5%. Surgery was continued after scanning in all of these cases, resulting in a reduction of final tumor volume from 21% to 12%. Hatiboglu et al[9] reported on a significant tumor volume reduction due to

TABLE 4. Tumor Volume Extent of Resection for Each Language Deficit Group[a]

Extent of Tumor Volume Resection (EOR in %)	Deficit Groups[b]			
	A	B	C	D
100	8	3	2	0
99.9-98.0	2	0	0	0
97.0-95.0	0	0	0	0
94.9-90.0	3	0	1	0
< 90.0	10	3	0	0
Total	23	6	3	0

[a]EOR, extent of resection.
[b]Group A, no postoperative aggravation of language deficits; group B, mild postoperative language deterioration then back to baseline function at discharge; group C, postoperative language deterioration, improved until discharge; group D, postoperative language deterioration without improvement until discharge.

intraoperative high-field MRI. Further resection was here performed in 47% after iMRI. The percentage of final GTR was high with 66%. The availability of functional data integrated in the navigation and iMRI might influence the surgical strategy in a way that surgery is performed more carefully until the first iMRI resection control. However, the surgical concept in clinical practice remains best possible tumor resection before considering resection control. This is supported by the fact that the surgeon's estimation was correct in 68.8%, in which surgery was not continued after iMRI, either because of initial GTR (34.38%) or close relation to eloquent structures (34.38%). It is hard to consider whether iMRI and update of the navigation or the integration of fMRI and fiber tractography has more impact on glioma surgery. Most likely, it is the combination of the strategies. However, in our opinion, iMRI is a potent tool for resection control, neuronavigation with integrated functional information and its intraoperative update helpful for the preservation of neurological function. For selected cases, fiber tractography in combination with intraoperative electrostimulation or intraoperative application of fMRI with awake surgery should still be considered.

DTI-Based Fiber Tractography

DTI-based fiber tractography has become a feasible method for visualization of white matter tracts in the brain. In particular, tractography of the corticospinal tract is well established in the clinical and surgical workflow. Although it enables us to visualize the normal course and displacement of white matter tracts around a tumor, as well as widening of fiber bundles due to edema or tumor infiltration,[12,15-18] there are still challenges related to the reconstruction of fiber bundles in the immediate vicinity of

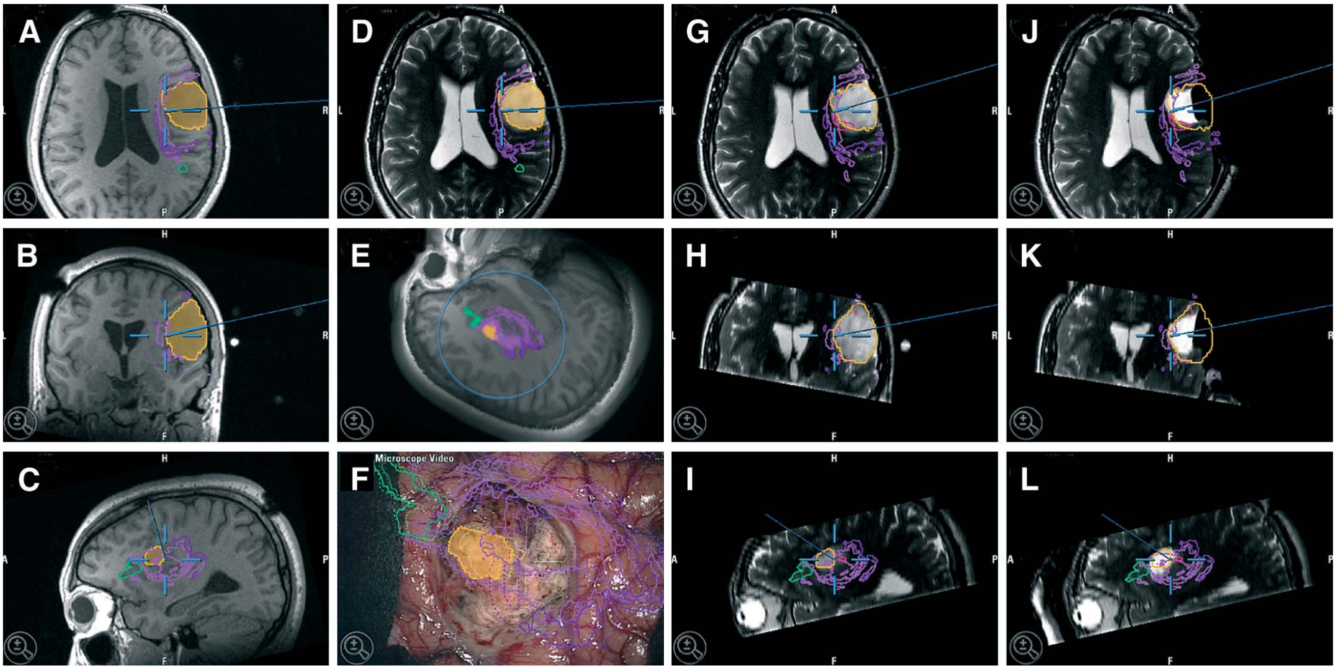

FIGURE 4. *Clinical case.* **A-F**, *navigation screenshot: MRI (performed before skin incision) used for registration displayed in multiple sets.* **A-C**, *T1-weighted images (axial, coronal, sagittal view).* **D**, *T2-weighted axial image.* **E**, *T1-weighted image probe's eye view.* **F**, *microscope view during tumor resection.* **G-L**, *navigation screenshot: MRI for registration (***G-I***) and iMRI for resection control (***K-L***) displayed in multiple sets for direct correlation; T2-weighted images.* **G-H**, *images before resection (axial, coronal, sagittal view);* **K-L**, *iMRI, displayed after re-registration intraoperatively and update of the navigation (axial, coronal, sagittal view). (Colors: tumor yellow; Broca and Wernicke area green; IOFF light purple; AF dark purple). iMRI, intraoperative magnetic resonance imaging; IOFF, inferior occipitofrontal fascicle.*

infiltrative tumors or distinct perifocal edema. The measured diffusion of water molecules according to different applied gradients and resulting estimated diffusion properties for each volume element is influenced by the presence of infiltrative tumor and surrounding edema as, for example, the anisotropy of diffusion is frequently reduced in these areas. Thus, in the vicinity of neuroepithelial tumors, the FA value is reduced in comparison with corresponding healthy tissue areas. Besides the FA value as threshold criterion, curvature of fiber tracts is also seen as an important parameter in the clinical fiber-tracking protocol. In the case of language pathways with its connection of 2 cortical areas and anatomical structure with fibers curving around the Sylvian fissure, tensor deflection-based algorithms can fail. For the 2 methods of DTI-based reconstruction of major white matter tracts—tensor deflection and CA algorithm—we recorded a deviation of approximately less than 5 mm. Each environment offers a different kind of seed region placement. Comparing the seed volume placements and definitions, there was no complete overlap in both environments, which causes the reconstruction results to be slightly different. With the use of the CA algorithm, we tried to overcome certain drawbacks of the tensor deflection algorithm, particularly considering language pathway reconstruction. Because the tensor deflection approach only uses the local tensor data for reconstruction of fiber tracks, the CA approach is goal-orientated and incorporates tensor information within the activation region's surrounding. Furthermore, splitting and merging fibers are handled appropriately. The CA algorithm enables us to find connections between seed and destination regions, which is not guaranteed by the tensor deflection approach. In this way, the CA approach is useful for finding connecting fibers between 2 regions. Because of the observed similarity, the CA algorithm results might be used for initial seed volume generation for the placement of seed regions and include and exclude regions for the US Food and Drug Administration-approved tensor deflection-based method routinely used in clinical practice. Besides DTI, there are several advanced techniques like high-angular resolution diffusion imaging, Q-Ball imaging, q-space imaging, and diffusion spectrum imaging to overcome the drawbacks of the second-order tensor model used for DTI. These advanced techniques allow the representation of multiple fiber orientations per voxel. Thereby, crossing fibers are being resolved. Because of the long acquisition times and high hardware-performance requirements, these advanced techniques are, up to now, not suitable for clinical use, which can be prospectively overcome by significant increasing MR gradient performance. Nevertheless, these MRI sequences (Q-Ball imaging, high-angular resolution diffusion imaging) are going to be evaluated, as well as other algorithms, to identify the best procedure for clinical practice satisfying the requirements of clinical use.

Limitations of Our Study

Only 6 gradient directions were provided in the DTI data set, because the examination started in the year 2003. According to current literature, at least 30 directions should be applied to obtain a more reliable estimation of the tensor.[31]

Our study compares 2 different DTI-based tracking algorithms during surgery for lesions in the vicinity of language-related sites and fibers. To evaluate the influence on morbidity, we assessed pre- and postoperative motor and language deficits, but did not include awake surgery or intraoperative stimulation methods. Although some studies correlating clinical outcome data questioned the accuracy and validity of DTI-based fiber tracking,[32] it has been shown that there is a significant correlation of fiber-tracking estimation with clinical outcome.[33]

Awake surgery and cortical and subcortical electrophysiological stimulation methods have been arranged in neurosurgical operating rooms to detect eloquent cortical areas and subcortical structures. The importance of intraoperative cortical mapping to contribute to minimizing postoperative morbidity in neurosurgical procedures has been established.[34,35] Thus, our future work will also include a complete neuropsychological testing (pre- and postoperatively) as well as intraoperative stimulation methods[5,36,37] and awake surgery.[38]

Considering the general problem of brain shift during surgery, mainly because of loss of cerebrospinal fluid or tumor volume reduction, this can be overcome by an update of the intraoperative image data. An update on functional data together with anatomical data is helpful in preserving eloquent cortical sites or fiber bundles. For the pyramidal tract, intraoperative update of the tracked fiber bundles is a feasible procedure.[18,39] However, an intraoperative update of DTI-based fiber tracking for language pathways requires an intraoperative fMRI to reliably detect the seed regions for the tracking procedure or nonlinear registration procedures, but these are still too time consuming to be considered for intraoperative use. Therefore, only the anatomical images were updated, whereas the fiber bundles corresponded to preoperatively tracked pathways. With the implementation of new algorithms, intraoperative update for language pathways is a matter of future work.

CONCLUSION

The combination of intraoperative DTI-based fiber tracking for language pathways and intraoperative high-field MRI contributes to maximally safe tumor resection with preservation of neurological function in glioma surgery. According to the common literature, this methodology is essential to achieve extended patient survival time.

Disclosures

This work was supported in part by the German Research Foundation (DFG NI568/3-1). Prof Nimsky is a scientific consultant for intraoperative imaging for BrainLab (Feldkirchen, Germany). The other authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

The authors set out to describe and compare 2 methodologies to recreate fiber tracts related to speech function in patients with tumors in or near eloquent speech areas. I agree with the authors that the tensor deflection methodology though robust relies heavily on the FA values to generate the underlying fiber tracts. They compare this to a connectivity algorithm (CA) which seems to incorporate tensor information within the areas of functional magnetic resonance imaging (fMRI) activation. The major caveat here is what does one use as a seed area in Wenicke's area as fMRI activation is not always well defined as in Brocas or in motor areas. The other important limitation with this study is that one does not know if the tracts generated were actually related to speech as none of the patients were awake or had any type of intraoperative stimulation in particular subcortical stimulation. Given these limitations the 4 month neurological complication rate was 4% overall. As the authors suggest generating reliable and reproducible diffusion tensor imaging (DTI) tracts related to speech function is a work in progress and we look forward to their future contributions in the future.

Sujit S. Prabhu
Houston, Texas

The paper by Kuhnt et al is at the leading edge of image-guided neurosurgery and the study appears to have been in the hands of investigators with more than ample experience in these techniques. Since the study group lacked controls (no patients were operated without fiber tracking), the study must be considered more a demonstration than a proof of efficacy. It is also difficult to know, as the authors noted, whether the favorable outcomes were primarily the result of (a) preoperative fMRI-DTI, (b) integrating preoperative fMRI-DTI into the neurosurgical navigation system, (c) registering pre-operative fMRI-DTI with intraoperatively updated anatomical MRI, (d) the intraoperative MRI itself, or (e) all of the above. It is also difficult to predict the extent to which these results may be generalized beyond the authors' own institution, given the currently limited availability and proprietary nature of the methods and materials used for the study (intraoperative MRI, BrainLab system, etc.). However, it can be said that whatever uncertainty there currently is regarding widespread application arises because the authors appear to be far ahead of the curve on image-guided neurosurgery and are most likely pointing the way for the field to follow.

Aaron Field
Madison, Wisconsin