Downloaded from https://academic.oup.com/neurosurgery/advance-article/doi/10.1093/neuros/nyaa463/6031391 by University of Western Ontario user on 21 December 2020

Predicting the Extent of Resection in Low-Grade Glioma by Using Intratumoral Tractography to Detect Eloquent Fascicles Within the Tumor

David Mato, MD, PhD[*]
Carlos Velasquez, MD, PhD[*]
Elsa Gómez, ST[‡]
Enrique Marco de Lucas, MD[§]
Juan Martino, MD, PhD[*]

[*]Department of Neurological Surgery, Hospital Universitario Marqués de Valdecilla and Fundación Instituto de Investigación Valdecilla, Santander, Spain; [‡]Department of Psychiatry, Hospital Universitario Marqués de Valdecilla and Fundación Instituto de Investigación Valdecilla, Santander, Spain; [§]Department of Radiology, Hospital Universitario Marqués de Valdecilla and Fundación Instituto de Investigación Valdecilla, Santander, Spain

Correspondence:
Juan Martino, MD, PhD,
Department of Neurological Surgery,
Hospital Universitario Marqués de
Valdecilla and Fundación Instituto de
Investigación Valdecilla,
Santander, Spain.
Email: juan.martino@hotmail.com

Received, June 14, 2019.
Accepted, August 12, 2020.

Copyright © 2020 by the
Congress of Neurological Surgeons

BACKGROUND: An early maximal safe surgical resection is the current treatment paradigm for low-grade glioma (LGG). Nevertheless, there are no reliable methods to accurately predict the axonal intratumoral eloquent areas and, consequently, to predict the extent of resection.

OBJECTIVE: To describe the functional predictive value of eloquent white matter tracts within the tumor by using a pre- and postoperative intratumoral diffusion tensor imaging (DTI) tractography protocol in patients with LGG.

METHODS: A preoperative intratumoral DTI-based tractography protocol, using the tumor segmented volume as the only seed region, was used to assess the tracts within the tumor boundaries in 22 consecutive patients with LGG. The reconstructed tracts were correlated with intraoperative electrical stimulation (IES)-based language and motor subcortical mapping findings and the extent of resection was assessed by tumor volumetrics.

RESULTS: Identification of intratumoral language and motor tracts significantly predicted eloquent areas within the tumor during the IES mapping: the positive predictive value for the pyramidal tract, the inferior fronto-occipital fasciculus, the arcuate fasciculus and the inferior longitudinal fasciculus positive was 100%, 100%, 33%, and 80%, respectively, whereas negative predictive value was 100% for all of them. The reconstruction of at least one of these tracts within the tumor was significantly associated with a lower extent of resection (67%) as opposed to the extent of resection in the cases with a negative intratumoral tractography (100%) ($P < .0001$).

CONCLUSION: Intratumoral DTI-based tractography is a simple and reliable method, useful in assessing glioma resectability based on the analysis of intratumoral eloquent areas associated with motor and language tracts within the tumor.

KEY WORDS: Low-grade glioma, Tractography, Diffusion tensor imaging, Awake craniotomy, Intraoperative electric stimulation

Neurosurgery 0:1–13, 2020 DOI:10.1093/neuros/nyaa463 www.neurosurgery-online.com

The current treatment paradigm for low-grade gliomas (LGGs) includes the maximal possible resection while preserving the neurological function.[1,2] This poses a surgical challenge considering their infiltration of white matter tracts[3,4] and the presence of functional areas within the tumor.[5,6]

Furthermore, a functional area within the tumor is one of the most important factors limiting the extent of resection (EoR).[1] Nevertheless, none of the currently available preoperative functional-imaging techniques[7,8] can be reliably used to predict the intratumoral functional areas, mainly due to their low predictive values and their limitation in assessing the functional subcortical anatomy.[9] Nevertheless, diffusion tensor imaging (DTI)-tractography provides a good correlation between

ABBREVIATIONS: 3D, 3-dimensional; **AF,** arcuate fasciculus; **DTI,** diffusion tensor imaging; **EoR,** extent of resection; **FA,** fractional anisotropy; **FAT,** frontal aslant tract; **fMRI,** functional MRI; **GTR,** gross total resection; **IES,** intraoperative electrical stimulation; **IFOF,** inferior fronto-occipital fasciculus; **ILF,** inferior longitudinal fasciculus; **KPS,** Karnofsky performance scale; **LGG,** low-grade glioma; **NPV,** negative predictive value; **OS,** overall survival; **PPV,** positive predictive value; **PT,** pyramidal tract; **ROI,** region of interest; **SLF,** superior longitudinal fasciculus

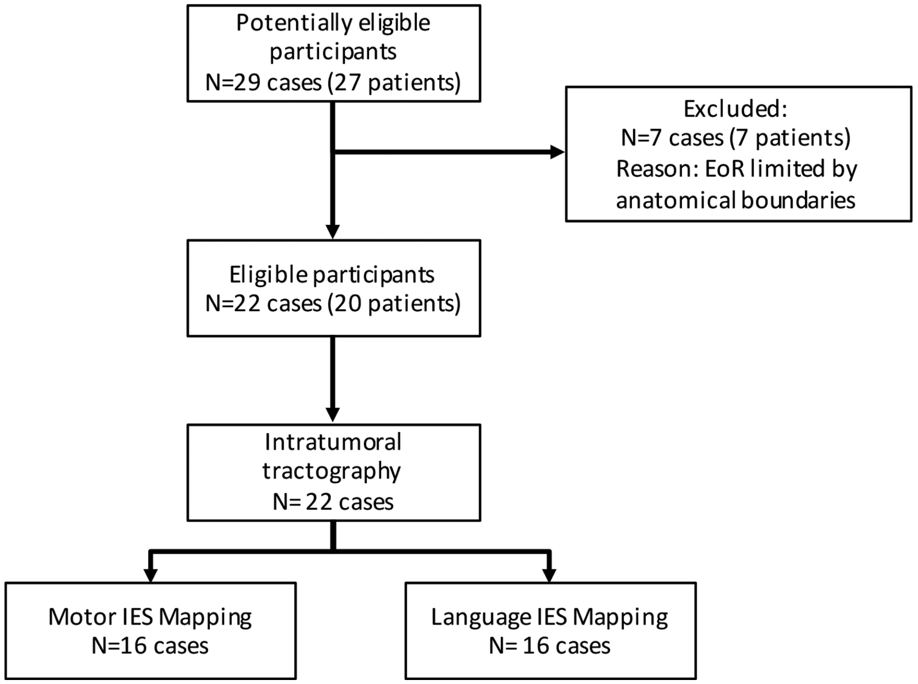


FIGURE 1. *Flow diagram of participants. The inclusion criteria were: 1) age > 18 yr, 2) tumor affecting an eloquent area, 3) IES with an asleep-awake-asleep technique, 4) maximal functional-based resection, 5) histological confirmation of LGG WHO Grade II. Cases in which the EoR was limited by anatomical/structural boundaries were excluded. The tumor affected both, language and motor areas, in 10 cases. All participants gave their informed consent to participate and all procedures were approved by the Committee of Human Research, and all research was conducted according to the Declaration of Helsinki.*

the reconstructed tracts and the subcortical intraoperative electrical stimulation (IES).[10-12]

In this study, we describe the functional predictive value of intratumoral eloquent subcortical tracts, which mark the limits of the EoR, by using a preoperative intratumoral DTI-tractography protocol in patients with LGG. In addition, we assessed the tumor resectability based on the presence of intratumoral functional areas.

METHODS

Participants and Study Design

A series of 22 surgical procedures (20 patients) for resection of LGG in eloquent areas[13] with sensorimotor mapping,[14] performed between July 2009 and July 2015 in a single institution, were retrospectively included in the analysis according to the criteria specified in Figure 1. Demographic and clinical features were collected, and all patients underwent a pre and postoperative neuropsychological assessment.

Neuroimaging and DTI Intratumoral Tractography

All patients underwent pre and postoperative brain magnetic resonance imaging (MRI) including functional MRI (fMRI) and DTI sequences as specified in Figure 2.

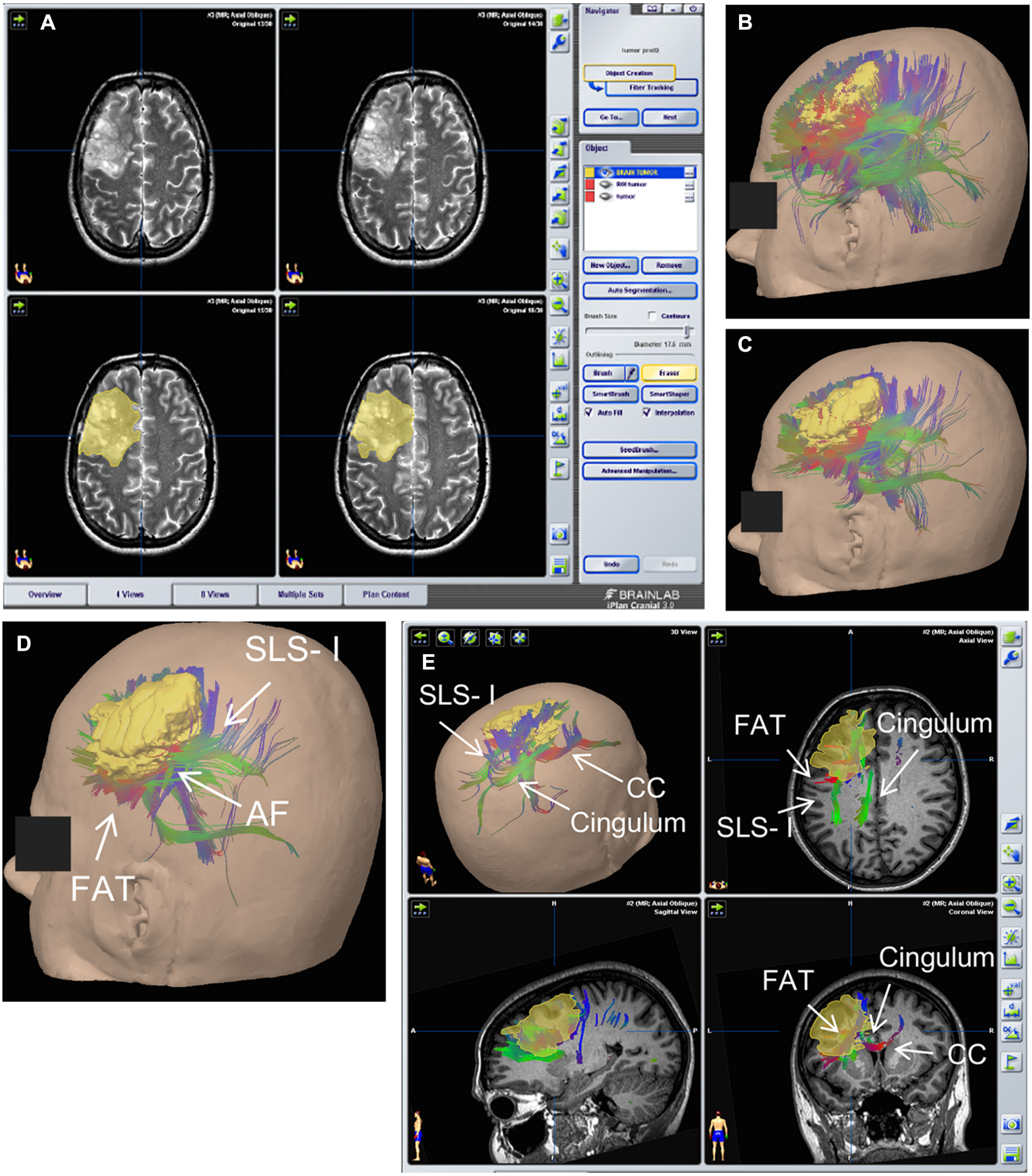
Tumor volumetrics and EoR were calculated by using manual tumor segmentation on the BrainLab Cranial Navigation Station (BrainLab AG, Munich, Germany) as described in Figure 2.[15] The DTI-based intratumoral tractography was obtained retrospectively for all patients by using a single region of interest (ROI) approach as illustrated in Figure 2. Initially, the fractional anisotropy (FA) threshold was set at 0.1 in all cases[16] and was progressively increased until the intratumoral white matter tracts were identified based on previously described anatomical landmarks.[17,18] This protocol was applied to the postoperative MRI in a similar manner, by using the residual tumor the only seed region.

Surgical Procedure and Reference Standard Test

All cases were operated on with an asleep-awake-asleep technique with sensorimotor and language cortical and subcortical electrical mapping, a method described extensively by our and other groups.[19] For the main tracts studied the expected response is detailed in Table 1.[20,21]

Intraoperative functional areas identified were located in the preoperative DTI-tractography images. A tract was considered to be a functional limit restraining further tumor resection when met the following criteria: 1) the distance between the point positive for motor or language function identified by IES and the reconstructed tract was <1 cm,[10] and 2) the same tract was reconstructed on the postoperative MRI by using the residual tumor as ROI.

Downloaded from https://academic.oup.com/neurosurgery/advance-article/doi/10.1093/neuros/nyaa463/6031391 by University of Western Ontario user on 21 December 2020



Downloaded from https://academic.oup.com/neurosurgery/advance-article/doi/10.1093/neuros/nyaa463/6031391 by University of Western Ontario user on 21 December 2020

FIGURE 2. *Illustrative case showing intratumoral tractography process. Intratumoral tractography was performed as follows:* **A**, *The tumor ROI was generated on the BrainLab Cranial Navigation Station (BrainLab AG, Munich, Germany), by using manual segmentation on the basis of 300-slices fluid-attenuated inversion-recovery axial sequences. The EoR was determined by tumor-volume segmentation of the pre- and 3 mo postoperative MRIs scans. The EoR was calculated as: (preoperative tumor volume - postoperative tumor volume)/preoperative tumor volume.* **B**, *A single-ROI approach was applied to initiate the fiber tracking algorithm by using tumoral volume as the only seed region and all axonal fibers were detected in both anterograde and retrograde directions according to each voxel´s main eigenvector within the ROI. Initially, the FA threshold was set at 0.1 in all cases. Besides, the minimum length was 40 mm and the maximal angulation was 20°.* **C**, *The FA threshold was progressively increased, as used in this picture where the FA threshold was 0.16.* **D**, *Final reconstruction using FA threshold 0.2. SLS-I, FAT, cingulum, and AF can be identified.* **E**, *To complete the tracts analysis different projections of the 3-dimensional (3D) reconstruction were used and axonal anatomy were also studied in axial, coronal, and sagittal planes. All MRI studies were performed on a 3.0-T magnetic resonance system using a 8-channel head coil (Achieva 3.0T; Philips Healthcare, Best, The Netherlands). A DTI with 64 difusion encoding directions was obtained by using multislice single-shot spin-echo echo-planar imaging (EPI). The spin-echo EPI acquisition parameters were as follows: diffusion sensitization = 1300 s/mm^2, repetition time = 9577 milliseconds, echo time = 77 milliseconds, voxel size = 2 mm^3; and matrix = 224 · 224.*

TABLE 1. Expected Response for the Main Tracts After EIS

White matter tract	Response expected
PT	contralateral movement
AF	phonemic paraphasia
IFOF	semantic paraphasia
ILF	semantic paraphasia
SLF-I	speech apraxia
SLF-II	dysarthria
SLF-III	anarthria
FAT	speech arrest
UF	semantic paraphasia
Subcallosal fasciculus	speech arrest
Cingulum	memory
Frontal-accumbens	planning and deciding

UF: Uncinate fasciculus.

Statistical Analysis

Frequency distributions and summary statistics were calculated for all variables. A Kolmogorov-Smirnov test was used to study the distribution of each variable and P-P and Q-Q charts were used to confirm it. The majority did not follow a normal distribution, and non-parametric tests were used for some of the comparisons.

The independent variable of interest was the identification of each tract within the tumor in the preoperative DTI tractography. The endpoint of the study was the identification of motor or language areas within the tumor during surgery. A logistic regression model and a Fisher's exact test were used to determine the relationship between the outcome variables and quantitative and qualitative variables, respectively. Besides, a multivariate analysis was performed in order to analyze for confounders. A significance level of 5% ($P < .05$) was accepted in all cases. SPSS software version 15.0 (SPSS, United Kingdom) was used for the statistical analysis.

RESULTS

The patient and tumor features are detailed in Table 2.

Intratumoral DTI-Based Tractography and IES

Motor and language functional areas were affected by the tumor in 16 cases each, and in 10 patients the tumor was located in areas with combined, motor and language, function.

TABLE 2. Demographic and Clinical Features

	Motor function cohort (%)	Language function cohort (%)
Age	42 yr (33-61)	45 yr (35-61)
Gender (male/female)	8 (50)/8 (50)	9 (56)/7 (44)
KPS	88% (70-100)	89% (70-100)
Tumor location		
Frontal		
SMA	10 (R: 1, L: 9) (63)	9 (L: 9) (56)
LPMC/FO	4 (R: 2, L: 2) (25)	1 (L: 1) (6)
PCG	2 (R: 2) (12)	
Temporal		
Posterior temporal	–	6 (L: 6) (38)
Mean tumor volume	44,3 cc (6,8-218,6)	34,4 cc (6,8-96,4)
Histopathology		
Astrocytoma	6 (37,5)	10 (62)
Oligodendroglioma	10 (62,5)	6 (38)

R: Right; L: Left; SMA: Supplementary motor cortex; LPMC: Lateral premotor cortex; FO: Frontal operculum; PCG: Precentral gyrus.

The following tracts were identified: pyramidal tract (PT), arcuate fasciculus (AF), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), frontal aslant tract (FAT), superior longitudinal fasciculus (SLF) part I, III and III, subcallosal fasciculus, frontal-accumbens fasciculus, corpus callosum, uncinate fasciculus, and cingulum. Fibers of the reconstructed tracts were mainly located within the peripheral part of the tumor at the T1-hypointense area. Table 3 summarizes main tracts identified in each case preop- and postoperatively, the FA threshold used and intraoperative identification of the tracts by electrical subcortical stimulation, including the intensity used (mA). The correlation between the preoperative tractography and the IES with classic motor and language mapping for all the tracts is summarized in Table 4 and in the illustrative cases (Figures 3-5).

Motor Function Analysis

In 10 out of 16 subjects (62%) the PT was identified within the tumor in the preoperative DTI tractography with a positive predictive value (PPV) of 100% and an negative predictive

Downloaded from https://academic.oup.com/neurosurgery/advance-article/doi/10.1093/neuros/nyaa463/6031391 by University of Western Ontario user on 21 December 2020

TABLE 3. **Summary of Case Data**

	Tumor location (R/L)	Volume (ml)	Function Studied (M/L)	Preoperative FA threshold	Preoperative intratumoral fascicles	Subcortical stimulation (mA)	Postoperative FA threshold	Postoperative intratumoral fascicles
Case 1	SMA–Lft	21.7	M/L	0.2	–	–	NA	NA
Case 2	LPMC/FO–R	106.7	M	0.2	–	–	NA	NA
Case 3	SMA–Lft	11.1	M/L	0.18	–	–	NA	NA
Case 4	PCG–R	38.8	M	0.2	PT	+ (2.5)	0.2	PT
Case 5	SMA–Lft	29.6	M/L	0.2	PT	+ (2)	0.2	PT
Case 6	PCG–R	218.7	M	0.18	PT	+ (2.5)	0.2	PT
Case 7	SMA–Lft	33.8	M/L	0.2	PT	+ (2.5)	0.22	PT
Case 8	LPMC/FO–Lft	59.9	M	0.18	PT	+ (1.5)	0.18	PT
Case 9	SMA–Lft	26.4	M/L	0.2	PT	+ (2)	0.22	PT
Case 10	SMA–Lft	15.9	M/L	0.2	PT	+(1.5)	0.22	PT
Case 11	SMA–Lft	33.4	M/L	0.18	PT	+ (2)	0.2	PT
Case 12	LPMC/FO–R	15.2	M	0.22	PT	+ (2)	0.2	PT
Case 13	SMA–Lft	6.8	M/L	0.22	–	–	NA	NA
Case 14	SMA–R	58.3	M	0.2	PT	+ (1.5)	0.2	PT
Case 15	LPMC/FO–Lft	30.1	M/L	0.18	IFOF	+ (2.5)	0.18	IFOF
Case 16	SMA–Lft	22	M/L	0.18	–	–	NA	NA
Case 17	TEMP–Lft	47.7	L	0.18	ILF	+ (2)	0.22	ILF
Case 18	TEMP–Lft	39.3	L	0.2	IFOFILF	+ (3)–	0.2	IFOF
Case 19	TEMP–Lft	49.2	L	0.18	AFILF	+ (2.5)+ (2.5)	0.18	AFILF
Case 20	TEMP–Lft	96.4	L	0.22	IFOF	+ (2)	0.2	IFOF
Case 21	TEMP–Lft	19	L	0.22	IFOFAFILF	+ (1)–+ (1)	0.2	IFOFAFILF
Case 22	TEMP–Lft	69.1	L	0.21	IFOFAFILF	+ (1.5)–+ (1.5)	0.2	IFOFAFILF

R: Right; Lft: Left; SMA: Supplementary motor cortex; LPMC: Lateral premotor cortex; FO: Frontal operculum; PCG: Precentral gyrus; M: motor; L: language; NA: not applicable.

TABLE 4. **Predictive Functional Values of the Most Significant White Matter Tracts Reconstructed in the Intratumoral Tractography**

White matter tract	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*P* value
PT	100	100	100	100	.00003
AF	100	87	33	100	.188
IFOF	100	100	100	100	.00003
ILF	100	91	80	100	.003
SLF-I	0	94	0	100	$>$.05
SLF-II	100	100	100	100	$>$.05
SLF-III	0	88	0	100	$>$.05
FAT[a]	*UD*	81	0[b]	100[b]	$>$.05
UF[a]	*UD*	94	0[b]	100[b]	$>$.05
CC[a]	*UD*	38	0[b]	100[b]	$>$.05
Subcallosal fasciculus	100	60	17	100	$>$.05
Cingulum[a]	*UD*	69	0[b]	100[b]	$>$.05
Frontal-accumbens fasciculus[a]	*UD*	69	0[b]	100[b]	$>$.05

NPV: Negative predictive value; PPV: Positive predictive value; UF: Uncinate fasciculus; CC: Corpus callosum.

[a] tracts whose functions have not been properly assessed intraoperatively, results cannot be considered meaningful; *UD*: undefined.

[b] results expected due to the lack of proper intraoperative task.

value (NPV) of 100%. Using a multivariate logistic regression model adjusted by sex, age, preoperative neurological deficits, handedness, tumor recurrence, tumor side, tumor location, and histopathology, the result was also statistically significant (p 1/4 0.002).

Language Function Analysis

The presence of IFOF, AF, and ILF in the preoperative DTI tractography, showed significant concordance with IES (Table 4) and significant predictive values for EoR.

Downloaded from https://academic.oup.com/neurosurgery/advance-article/doi/10.1093/neuros/nyaa463/6031391 by University of Western Ontario user on 21 December 2020

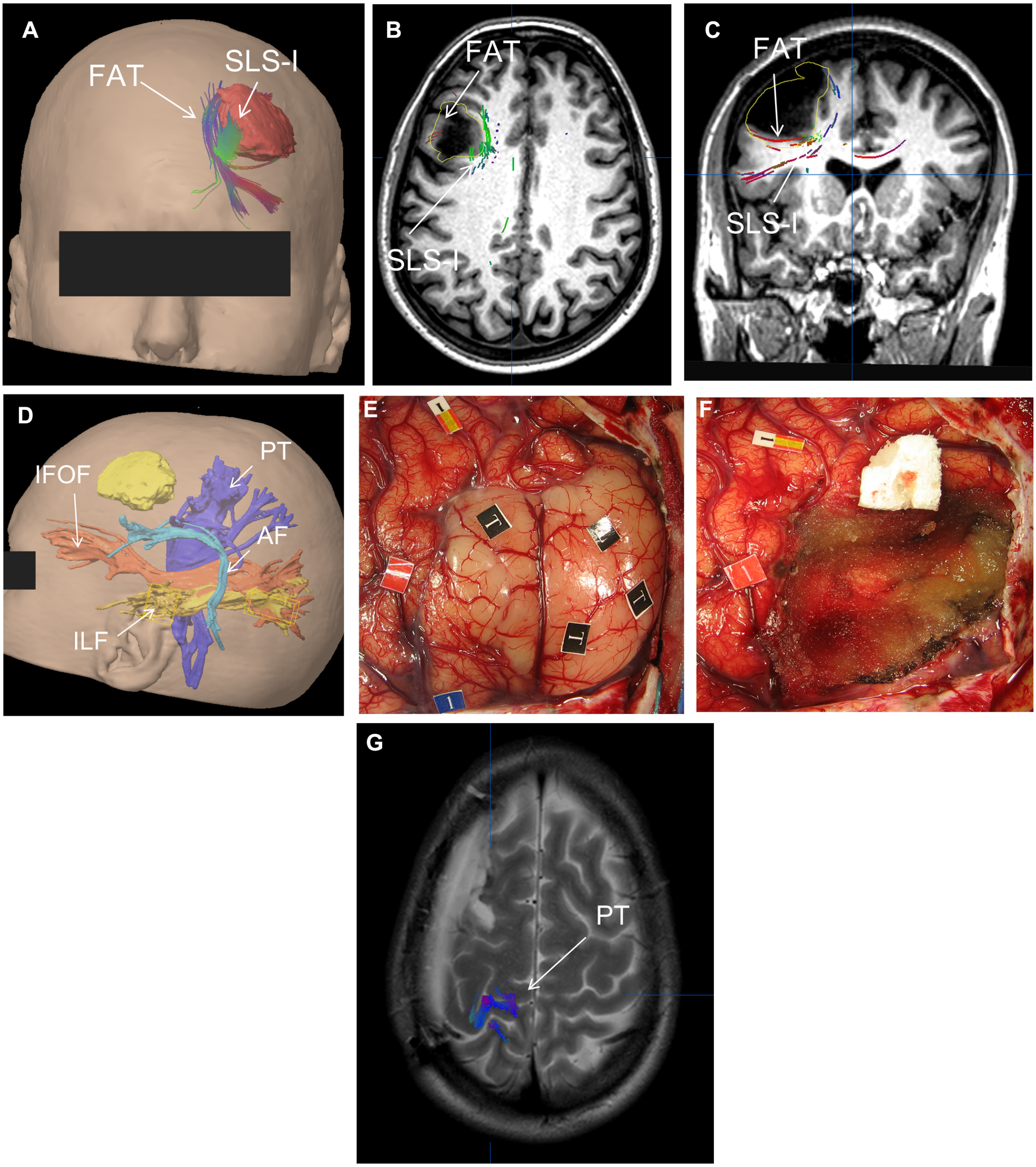
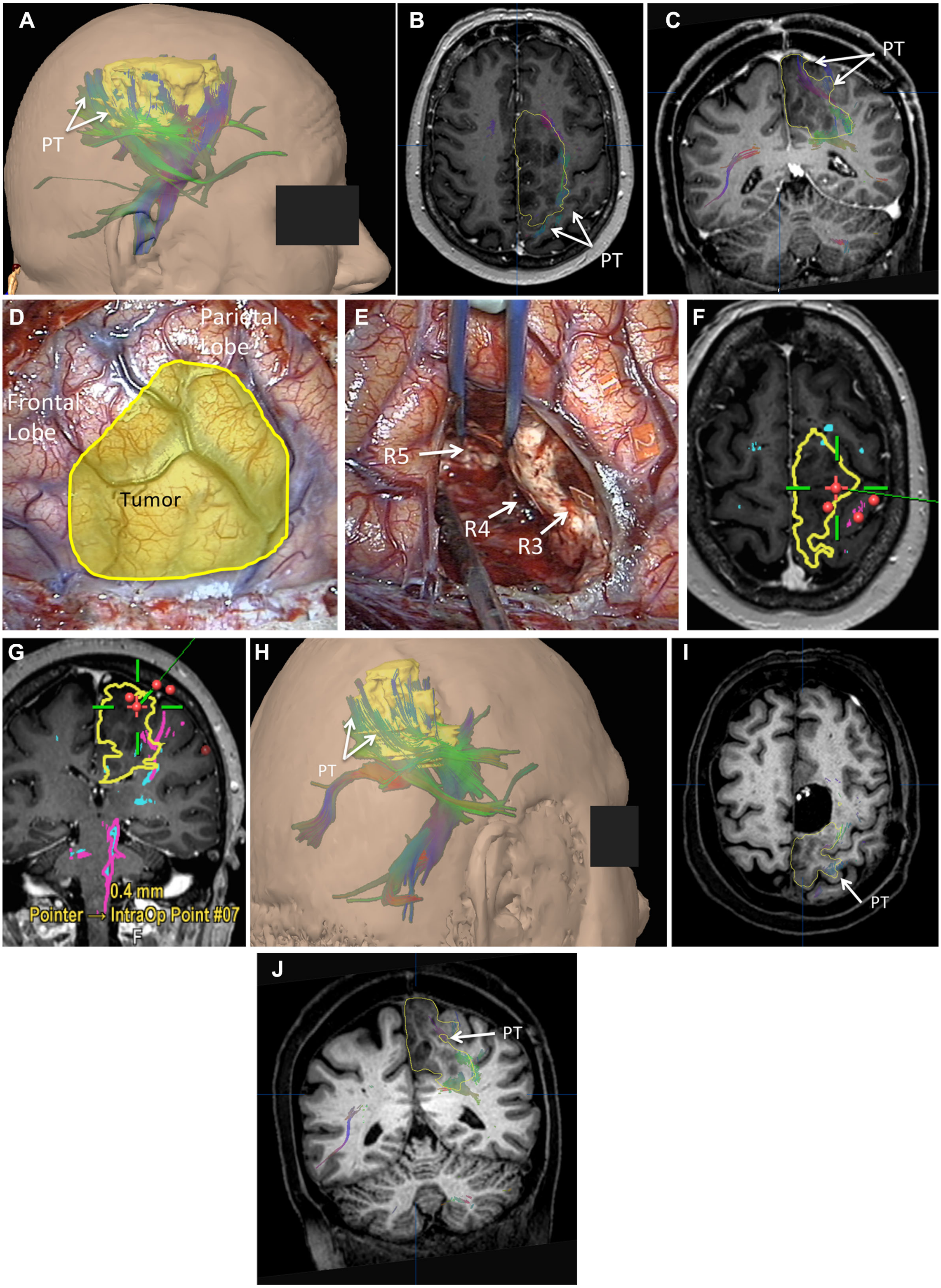


FIGURE 3. *Illustrative case of GTR. A 41-yr-old right-handed female patient with a left frontal LGG who presented an episode of seizures.* **A**, *Presurgical intratumoral tractography in which the FAT and SLS-I were identified.* **B** *and* **C**, *Axial and coronal MRI slices showing FAT and SLS-I fibers running within the inferior pole of the tumor.* **D**, *Presurgical reconstruction of PT, IFOF, AF, and ILF using atlas-based ROI selection, where no direct relation with the tumor is seen.* **E**, *Cortical functional map after IES depicting the tumor boundaries (T), a "speech arrest" area in the ventral premotor cortex (2,5 mA) (Flag 1); Red 1 = right arm proximal extension in the supplementary motor area; and Blue 1 = dizziness in the posterior part of the superior frontal gyrus.* **F**, *Intraoperative picture after GTR, with no subcortical functional limits after electrical stimulation.* **G**, *Postoperative T2-WI showing distance between the posterior margin of tumor cavity and PT.*

Downloaded from https://academic.oup.com/neurosurgery/advance-article/doi/10.1093/neuros/nyaa463/6031391 by University of Western Ontario user on 21 December 2020



[redacted]

[redacted]

Downloaded from https://academic.oup.com/neurosurgery/advance-article/doi/10.1093/neuros/nyaa463/6031391 by University of Western Ontario user on 21 December 2020

FIGURE 4. *Illustrative case of motor function. A 61-yr-old right-handed female patient with a right frontal LGG who presented with an episode of seizures.* **A**, *Presurgical intratumoral tractography depicting the tumor infiltration of the most cranial portion of the PT.* **B** *and* **C**, *Axial and coronal MRI slices showing PT fibers running within the posterior and most cranial part of the tumor.* **D**, *Intraoperative image showing the tumor boundaries (marked with a yellow line) and anatomical landmarks before tumor.* **E**, *Intraoperative picture after tumor resection showing the subcortical functional limits related to the PT: Red 3 = movement of left toes; Red 4 = movement of the left hand; Red 5 = left first toe flexion; Red 6 = left hand finger flexion.* **F** *and* **G**, *Intraoperative snapshots of the image guidance system showing the location of the subcortical functional limits related to the PT.* **H**, *Postoperative intratumoral tractography, the PT was reconstructed, as expected, by using the residual tumor as the only ROI.* **I** *and* **J**, *Axial and coronal MRI showing PT fibers within the residual tumor after intratumoral DTI reconstruction.*

The IFOF was preoperatively reconstructed within the tumor in 31% of the cases and showed a PPV of 100% and an NPV of 100%. The AF was preoperatively reconstructed within the tumor in 18% of the cases and the preoperative intratumoral identification of the AF had a PPV of 33% and an NPV of 100%. The ILF was preoperatively reconstructed within the tumor in 38% of the cases with a PPV of 80% and an NPV of 100% (Table 4). These results were also statistically significant after using a multivariate logistic regression model (p 1/4 0.002; p 1/4 0.002 and p 1/4 0.002 for AF, IFOF and ILF, respectively).

The identification in the preoperative DTI-tractography of any of the other tracts studied was not predictive of the positive findings in IES mapping ($P > .05$).

EoR and Oncological Outcome

The mean EoR in the complete cohort (22 cases) was 76% (range: 24%-100%) with a mean residual tumor volume of 16.4 cm^3(range 0-167.5 cm^3).

In 5 cases (23%), a gross total resection (GTR) was achieved. None of the tracts with high predictive functional values (PT, AF, IFOF, and ILF) were identified in these cases. In the remaining cases, a subtotal (36%) or a partial (41%) resection was achieved. Among these cases, the PT, the IFOF, the AF, and the ILF were reconstructed in 10 (45%), 5 (23%), 3 (14%), and 5 (23%) cases, respectively. In all of them, these findings correlated with the IES mapping and, therefore, limited the extend of resection.

The patients with at least one of the tracts with high predictive functional values in the preoperative intratumoral tractography had an EoR and a residual tumor volume of 67% (range 23%-94%) and 21.24 cm^3 (range 0.8-167 cm^3), respectively. Of these cases, we must point out the one with such a big residual tumor (167.5 cm^3), coincident with the lowest EoR (24%), where the PT was identified almost in the middle of the lesion. As opposed to the patients with absence of these tracts within the tumor, who had a complete resection without any residual tumor. These differences were statistically significant ($P < .0001$).

Functional and Neurological Outcomes

No significant differences were found in pre- and postoperative Karnofsky performance scale (KPS) in patients with and without intratumoral highly functional predictive tracts (mean postoperative KPS = 86%, mean preoperative KPS = 88%; $P > .05$). No patients presented language deficits when assessed 6 mo postoperatively and only 2 patients presented a new mild-moderate postoperative motor deficit.

DISCUSSION

DTI-Based Intratumoral Tractography

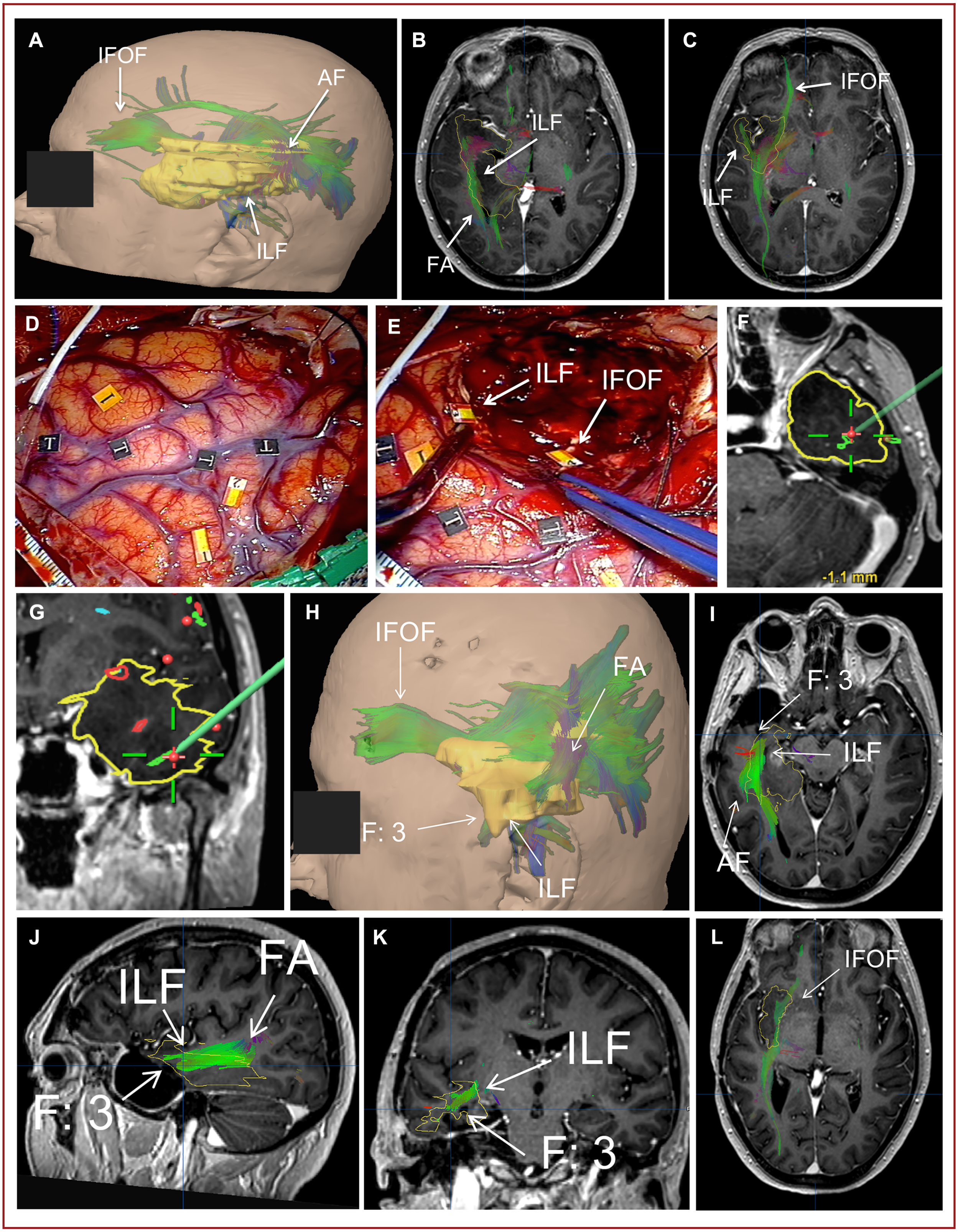
The DTI-based tractography has become a well-established clinical tool with applications including assessment of the subcortical preoperative anatomy, characterization of epileptic networks and study of the connectome in neurodegenerative disorders.[17,22-25] DTI-tractography's limitations are also widely described. It's well known that its specificity and sensitivity could be influenced by numerous factors leading to false positives and negatives findings.[26,27]

Its user-dependency is one of these factors,[28] and several approaches have been proposed to minimize it: atlas-based ROI selection,[29] fMRI-based ROI selection,[30-32] and automatized tractography.[33] Nevertheless, a protocol based on the tumor segmented volume as the only ROI has never been described and its application in the operative management of LGG is unknown. This method takes advantage of the infiltrative nondestructive nature of LGG to reconstruct the tracts within the tumor resulting in high predictive values. Therefore, this new protocol drastically simplifies the arduous task of reconstructing each tract, especially those infiltrated by the glioma, where severe anatomical distortion and functional reorganization of the cortex can lead to false negative results, even with the use of atlas- or fMRI-based ROI selection and automatized tractography.

IES remains as the "gold standard" for assessing brain function and its concordance with the neuronavigated tractography has been used to validate the reconstructed tracts. In order to compensate for the brain shift effect, a distance threshold of 8 to 15 mm between the neuronavigated tract and the location of positive subcortical stimulation is commonly used.[10-12]

Furthermore, peritumoral edema, tumoral infiltration and structural distortion lead to a diminished FA, below the threshold commonly used in clinical tractography protocols for presurgical planning, resulting in potential false negatives.[34-36] Although, reducing the threshold of the FA might help to overcome this limitation,[16,36] this could increase the risk of false positives.[27] High-definition tractography has been also used to solve this problem in high-grade gliomas.[37] In our study, we avoided this problem by progressively increasing the FA until we were able to recognize the tracts based on subcortical anatomical landmarks.

Downloaded from https://academic.oup.com/neurosurgery/advance-article/doi/10.1093/neuros/nyaa463/6031391 by University of Western Ontario user on 21 December 2020



Downloaded from https://academic.oup.com/neurosurgery/advance-article/doi/10.1093/neuros/nyaa463/6031391 by University of Western Ontario user on 21 December 2020

FIGURE 5. *Illustrative case of language function. A 53-yr-old right handed female patient with a left temporal LGG who presented with an episode of seizures.* **A**, *Presurgical intratumoral tractography 3D reconstruction in which the IFOF, the ILF, and the AF were identified.* **B** *and* **C**, *Axial MRI slices showing intratumoral tractography in detail, were fibers of ILF, AF, and IFOF were identified running within the tumor.* **D**, *Cortical functional map after IES depicting the tumor boundaries (T) and a "speech arrest" area in the ventral premotor cortex (Flags 1 and 2).* **E**, *Intraoperative picture after tumor resection showing the subcortical functional limits: Flag 3 = anomia (ILF); Flag 4 = anomia (IFOF). No functional limit related to the AF was identified, despite having been reconstructed preoperatively, so it was considered a false positive result.* **F** *and* **G**, *Intraoperative snapshots of the image guidance system showing the location of the functional limit related to the ILF.* **H**, *Postoperative intratumoral tractography. Flag 3 (F:3) position is marked. The IFOF, the ILF, and the AF were identified after using the residual tumor as the only ROI. It was considered that the false negative of the AF was conditioned by the anatomical arrangement of the tracts in this area, since in the lower portion of the temporal lobe its covered by the ILF.* **I-K**, *Axial, sagittal and coronal MRI showing position of flag 3 (F:3) and fibers of the ILF and AF.* **L**, *Axial MRI showing fibers of the IFOF within the residual tumor.*

Resectability Prediction Value

It's widely accepted that the EoR is a major predictor of overall survival (OS) and progression free survival and that an increment in EoR is associated with a longer life expectancy in gliomas and with a better seizure control.[15,38-41]

The most important factor limiting the EoR in glioma surgery is the eloquence in the cortical and subcortical areas related to the tumor.[13] Consequently, a method to reliably assess the functional areas within the tumor will significantly impact the EoR.

Recently, efforts oriented to predict the EoR in patients with LGG and HGG have resulted in the integration of multimodal tools in their management.[42] Resectability indexes, maps, and scores for gliomas have been developed by using different approaches: preoperative clinical and radiological variables,[43] tumor residue analysis,[44] and expert opinion.[45-47] Nevertheless, a comprehensive analysis of the subcortical eloquent structures is not commonly used as a major factor when assessing resectability. Considering the high predictive value of the intratumoral DTI-based tractography, described here, this approach could add significant data when integrated into these resectability prediction approaches.

The use of the preoperative tractography to predict the EoR in LGG has been previously described. Castellano et al, after using an anatomy-based ROI tractography approach to study the PT, the IFOF, and the SLF, concluded that the infiltration of the PT or the IFOF was associated with a low probability of achieving a GTR.[48] In a similar study, Bertani et al, described that the tractographic reconstruction of the IFOF predicts the EoR in tumors anatomically related to this tract.[49] In addition, based on a case report, Freyschlag et al, described how a combination of complex DTI processing may be able to predict function and EoR in a patient a left temporoparietal glioma.[50]

Nevertheless, both case series studies[48,49] included a heterogenous cohort of patients with biologically different tumors. This is relevant considering the relation between the tumor and adjacent tracts, ie, HGG will tend to destroy the surrounding tracts and DNETs will tend to displace them, rather than encompassing them within the tumor volume. Besides, their results were not validated by assessing the correlation with subcortical IES mapping.

In our series, a negative intratumoral tractography for the main tracts (PT, AF, IFOF, or ILF) predicted a GTR and whenever these tracts were reconstructed preoperatively, achieving a GTR was not possible. Moreover, in the group with a positive preoperative intratumoral tractography the mean extend of resection was considerably below the threshold of >80% to 91%, needed to achieve seizure control.[40,41]

Functional Predictive Value

The mean OS in patients with LGG is 14 yr after early resection,[39] and long lasting neurological deficits following glioma resection may significantly affect quality of life.[1] Therefore, the clinical challenge in the management of these patients is to avoid any neurological deficit.

Although, DTI-based tractography is not a functional neuroimaging method per se and it only studies the subcortical structural anatomy, it can be indirectly used to assess the subcortical function. Here, we show that a significant concordance between the tractography and the IES subcortical mapping can be achieved by using a probabilistic intratumoral-seeded tractography protocol. Other preoperative neuroimaging methods available, as fMRI, have failed in reliably predicting functional areas in presurgical language mapping.[9]

Patient Preoperative Counseling

The preoperative assessment of patients with gliomas in eloquent regions, includes a comprehensive discussion with the patient regarding the expected postoperative deficits and EoR. Therefore, methods to accurately estimate these outcome measures are particularly useful for patient preoperative counseling.[51]

The intratumoral DTI-based tractography can be used to help counseling patients by providing them with realistic expectations about EoR and postoperative neurological deficit. Besides, it could help to establish the need of referring the patient to a specialized center, with an acceptable rate of surgery-related deficits.[52]

Limitations

It is important to take into account some limitations of this protocol when considering applying this technique. First, this approach is only applicable to LGG due to their specific biologically determined growth pattern.[4] Furthermore, when the tumor resectability is limited by anatomical/structural nonfunctional

Downloaded from https://academic.oup.com/neurosurgery/advance-article/doi/10.1093/neuros/nyaa463/6031391 by University of Western Ontario user on 21 December 2020

factors, ie, lenticulostriate arteries in the limen insulae in insular LGG,[53] this approach alone is not suitable to reliably predict the EoR.

Moreover, the significance of the sensitivity, specificity and predictive values will be affected by the intraoperative tasks assessed. For example, in the illustrative case showed in Figure 3, the nonfunctionality of the FAT could be related to the choice of speech arrest as the expected effect of stimulation (Table 1). However, stimulation of the FAT could cause perseverations/semantic paraphasia or even sentence planning disturbances.[54,55] Furthermore, if specific tasks, as memory, are not intraoperatively assessed, structures as the cingulum would not be recognized as a functional limit, despite being present. Consequently, our study cannot be conclusive about those tracts which have not been properly stimulated intraoperatively.

Finally, the predictive values of a test are also related to the prevalence and in our study, the prevalence was conditioned by the anatomy of the tracts and the locations of the tumors.

CONCLUSION

Intratumoral DTI-based tractography is a simple and reliable method, useful in assessing glioma resectability based on the analysis of intratumoral eloquent areas associated with motor and language tracts within the tumor boundaries. In our study, the presence of the PT, the AF, the IFOF, or the ILF, within the tumor predicted intratumoral subcortical eloquent areas and the EoR.

Funding

This study did not receive any funding or financial support.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Hervey-Jumper SL, Berger MS. Evidence for improving outcome through extent of resection. *Neurosurg Clin N Am*. 2019;30(1):85-93.
2. Mandonnet E, Wager M, Almairac F, et al. Survey on current practice within the European Low-Grade Glioma Network: where do we stand and what is the next step? *Neuro-Oncology Pract*. 2017;4(4):npw031.
3. Giese A, Bjerkvig R, Berens ME, Westphal M. Cost of migration: invasion of malignant gliomas and implications for treatment. *J Clin Oncol*. 2003;21(8):1624-1636.
4. Mandonnet E, Capelle L, Duffau H. Extension of paralimbic low grade gliomas: toward an anatomical classification based on white matter invasion patterns. *J Neurooncol*. 2006;78(2):179-185.
5. Skirboll SS, Ojemann GA, Berger MS, Lettich E, Winn HR. Functional cortex and subcortical white matter located within gliomas. *Neurosurgery*. 1996;38(4):678-685; discussion 684-5.
6. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. *N Engl J Med*. 2008;358(1):18-27.
7. Bogomolny DL, Petrovich NM, Hou BL, Peck KK, Kim MJJ, Holodny AI. Functional MRI in the brain tumor patient. *Top Magn Reson Imaging*. 2004;15(5):325-335.
8. Martino J, Honma SM, Findlay AM, et al. Resting functional connectivity in patients with brain tumors in eloquent areas. *Ann Neurol*. 2011;69(3):521-532.
9. Giussani C, Roux F-E, Ojemann J, Sganzerla EP, Pirillo D, Papagno C. Is preoperative functional magnetic resonance imaging reliable for language areas mapping in brain tumor surgery? Review of language functional magnetic resonance imaging and direct cortical stimulation correlation studies. *Neurosurgery*. 2010;66(1):113-120.
10. Zhu F-P, Wu J-S, Song Y-Y, et al. Clinical application of motor pathway mapping using diffusion tensor imaging tractography and intraoperative direct subcortical stimulation in cerebral glioma surgery: a prospective cohort study. *Neurosurgery*. 2012;71(6):1170-1184; discussion 1183-4.
11. Zolal A, Hejčl A, Vachata P, et al. The use of diffusion tensor images of the corticospinal tract in intrinsic brain tumor surgery: a comparison with direct subcortical stimulation. *Neurosurgery*. 2012;71(2):331-340; discussion 340.
12. Romano A, D'Andrea G, Calabria LF, et al. Pre- and intraoperative tractographic evaluation of corticospinal tract shift. *Neurosurgery*. 2011;69(3):696-705; discussion 704-5.
13. Duffau H, Capelle L. Preferential brain locations of low-grade gliomas. *Cancer*. 2004;100(12):2622-2626.
14. Martino J, Mato D, Marco de Lucas E, et al. Subcortical anatomy as an anatomical and functional landmark in insulo-opercular gliomas: implications for surgical approach to the insular region. *J Neurosurg*. 2015;123(4):1081-1092.
15. Smith JS, Chang EF, Lamborn KR, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. *J Clin Oncol*. 2008;26(8):1338-1345.
16. Bello L, Gambini A, Castellano A, et al. Motor and language DTI fiber tracking combined with intraoperative subcortical mapping for surgical removal of gliomas. *Neuroimage*. 2008;39(1):369-382.
17. Catani M, Howard RJ, Pajevic S, Jones DK. Virtual in vivo interactive dissection of white matter fasciculi in the human brain. *Neuroimage*. 2002;17(1):77-94.
18. Fernández-Miranda JC, Rhoton AL, Álvarez-Linera J, Kakizawa Y, Choi C, de Oliveira EP. Three-dimensional microsurgical and tractographic anatomy of the white matter of the human brain. *Neurosurgery*. 2008;62(Supplement 3):SHC989-SHC1028.
19. Martino J, Mato D, de Lucas EM, et al. Subcortical anatomy as an anatomical and functional landmark in insulo-opercular gliomas: implications for surgical approach to the insular region. *J Neurosurg*. 2015;123(4):1081-1092.
20. Duffau H, Peggy Gatignol ST, Mandonnet E, et al. Intraoperative subcortical stimulation mapping of language pathways in a consecutive series of 115 patients with grade II glioma in the left dominant hemisphere. *J Neurosurg*. 2008;109(3):461-471.
21. Duffau H. Stimulation mapping of myelinated tracts in awake patients. *Brain Plast*. 2016;2(1) 99-113.
22. Jellison BJ, Field AS, Medow J, Lazar M, Salamat MS, Alexander AL. Diffusion tensor imaging of cerebral white matter: a pictorial review of physics, fiber tract anatomy, and tumor imaging patterns. *AJNR Am J Neuroradiol*. 2004;25(3):356-369.
23. Luat AF, Chugani HT. Molecular and diffusion tensor imaging of epileptic networks. *Epilepsia*. 2008;49(s3):15-22.
24. Medina DA, Gaviria M. Diffusion tensor imaging investigations in Alzheimer's disease: the resurgence of white matter compromise in the cortical dysfunction of the aging brain. *Neuropsychiatr Dis Treat*. 2008;4(4):737-742.
25. Sigal T, Shmuel M, Mark D, Gil H, Anat A. Diffusion tensor imaging of corpus callosum integrity in multiple sclerosis: correlation with disease variables. *J Neuroimaging*. 2012;22(1):33-37.
26. Mandelli ML, Berger MS, Bucci M, Berman JI, Amirbekian B, Henry RG. Quantifying accuracy and precision of diffusion MR tractography of the corticospinal tract in brain tumors. *J Neurosurg*. 2014;121(2):349-358.
27. Campbell JSW, Pike GB. Potential and limitations of diffusion MRI tractography for the study of language. *Brain Lang*. 2014;131:65-73.
28. Pujol S, Wells W, Pierpaoli C, et al. The DTI challenge: toward standardized evaluation of diffusion tensor imaging tractography for neurosurgery. *J Neuroimaging*. 2015;25(6):875-882.
29. Leclercq D, Delmaire C, Menjot de Champfleur N, Chiras J, Lehéricy S. Diffusion tractography: methods, validation and applications in patients with neurosurgical lesions. *Neurosurg Clin N Am*. 2011;22(2):253-268.
30. Schonberg T, Pianka P, Hendler T, Pasternak O, Assaf Y. Characterization of displaced white matter by brain tumors using combined DTI and fMRI. *Neuroimage*. 2006;30(4):1100-1111.

Downloaded from https://academic.oup.com/neurosurgery/advance-article/doi/10.1093/neuros/nyaa463/6031391 by University of Western Ontario user on 21 December 2020

31. Staempfli P, Reischauer C, Jaermann T, Valavanis A, Kollias S, Boesiger P. Combining fMRI and DTI: a framework for exploring the limits of fMRI-guided DTI fiber tracking and for verifying DTI-based fiber tractography results. *Neuroimage*. 2008;39(1):119-126.
32. Kleiser R, Staempfli P, Valavanis A, Boesiger P, Kollias S. Impact of fMRI-guided advanced DTI fiber tracking techniques on their clinical applications in patients with brain tumors. *Neuroradiology*. 2010;52(1):37-46.
33. Zhang S, Correia S, Laidlaw DH. Identifying white-matter fiber bundles in DTI data using an automated proximity-based fiber-clustering method. *IEEE Trans Vis Comput Graph*. 2008;14(5):1044-1053.
34. Witwer BP, Moftakhar R, Hasan KM, et al. Diffusion-tensor imaging of white matter tracts in patients with cerebral neoplasm. *J Neurosurg*. 2002;97(3):568-575.
35. Goebell E, Paustenbach S, Vaeterlein O, et al. Low-grade and anaplastic gliomas: differences in architecture evaluated with diffusion-tensor MR imaging. *Radiology*. 2006;239(1):217-222.
36. Stadlbauer A, Nimsky C, Buslei R, et al. Diffusion tensor imaging and optimized fiber tracking in glioma patients: histopathologic evaluation of tumor-invaded white matter structures. *Neuroimage*. 2007;34(3):949-956.
37. Abhinav K, Yeh F-C, Mansouri A, Zadeh G, Fernandez-Miranda JC. High-definition fiber tractography for the evaluation of perilesional white matter tracts in high-grade glioma surgery. *Neuro Oncol*. 2015;17(9):nov113.
38. Roelz R, Strohmaier D, Jabbarli R, et al. Residual tumor volume as best outcome predictor in low grade glioma–A nine-years near-randomized survey of surgery vs. biopsy. *Sci Rep*. 2016;6(1):32286.
39. Jakola AS, Skjulsvik AJ, Myrmel KS, et al. Surgical resection versus watchful waiting in low-grade gliomas. *Ann Oncol*. 2017;28(8):1942-1948.
40. Xu DS, Awad A-W, Mehalechko C, et al. An extent of resection threshold for seizure freedom in patients with low-grade gliomas. *J Neurosurg*. 2018;128(4):1084-1090.
41. Still MEH, Roux A, Huberfeld G, et al. Extent of resection and residual tumor thresholds for postoperative total seizure freedom in epileptic adult patients harboring a supratentorial diffuse low-grade glioma. *Neurosurgery*. 2019;85(2):E332-E340.
42. Barone DG, Lawrie TA, Hart MG. Image guided surgery for the resection of brain tumours. *Cochrane Database Syst Rev*. 2014;2014(1):CD009685.
43. Spena G, D'Agata F, Panciani PP, Buttolo L, di Monale Bastia MB, Fontanella MM. Practical prognostic score for predicting the extent of resection and neurological outcome of gliomas in the sensorimotor area. *Clin Neurol Neurosurg*. 2018;164:25-31.
44. Hendriks EJ, Idema S, Hervey-Jumper SL, et al. Preoperative resectability estimates of nonenhancing glioma by neurosurgeons and a resection probability map. *Neurosurgery*. 2019;85(2):E304-E313.
45. Sonabend AM, Zacharia BE, Cloney MB, et al. Defining glioblastoma resectability through the wisdom of the crowd. *Neurosurgery*. 2016;80(4):1.
46. De Witt Hamer PC, Hendriks EJ, Mandonnet E, et al. Resection probability maps for quality assessment of glioma surgery without brain location bias. *PLoS One*. 2013;8(9):e73353. eCollection 2013.
47. Mandonnet E, Jbabdi S, Taillandier L, et al. Preoperative estimation of residual volume for WHO grade II glioma resected with intraoperative functional mapping. *Neuro Oncol*. 2007;9(1):63-69.
48. Castellano A, Bello L, Michelozzi C, et al. Role of diffusion tensor magnetic resonance tractography in predicting the extent of resection in glioma surgery. *Neuro-oncol*. 2012;14(2):192-202.
49. Bertani G, Carrabba G, Raneri F, et al. Predictive value of inferior fronto-occipital fasciculus (IFO) DTI-fiber tracking for determining the extent of resection for surgery of frontal and temporal gliomas preoperatively. *J Neurosurg Sci*. 2012;56(2):137-143.
50. Freyschlag CF, Kerschbaumer J, Pinggera D, Bodner T, Grams AE, Thomé C. Preoperative prediction of language function by diffusion tensor imaging. *Brain Inf*. 2017;4(3):201-205.
51. Jakola AS, Gulati S, Weber C, Unsgård G, Solheim O. Postoperative deterioration in health related quality of life as predictor for survival in patients with glioblastoma: a prospective study. *PLoS One*. 2011;6(12):e28592.
52. Krieg SM, Schnurbus L, Shiban E, et al. Surgery of highly eloquent gliomas primarily assessed as non-resectable: risks and benefits in a cohort study. *BMC Cancer*. 2013;13(1):51.
53. Velásquez C, Caballero H, Vazquez-Barquero A, et al. Insular gliomas with exophytic extension to the sylvian cistern: a glioma growth pattern that has gone previously unnoticed. *World Neurosurg*. 2016;87:200-206.
54. Corrivetti F, de Schotten MT, Poisson I, et al. Dissociationg motor-speech from lexico-semantic systems in the left frontal lobe: insight from a series of 17 awake intraoperative mappings in glioma patients. *Brain Struct Funct*. 2019;224(3):1151-1165.
55. Chernoff DL, Sims MH, Smith SO, et al. Direct electrical stimulation of the left frontal aslant tract disrupts sentence planning without affecting articulation. *Cogn Neuropsychol*. 2019;36(3-4):178-192.

COMMENTS

In this innovative paper, the authors propose tumor-seed tractography as a new way to assess white matter pathways in the planning of diffuse low-grade glioma (DLGG) resection. They elegantly demonstrated that the detectability of some intratumoral tracts, like the corticospinal tract, arcuate fasciculus, or inferior fronto-occipital fasciculus, correlated with a positive language and motor mapping of white matter and was predictive of lower chances to achieve a complete resection. One of the main advantages of this method is to provide a standardized process for dissecting preoperative tractograms of DLGG patients, paving the way towards multicenter studies on this topic. This being said, well known limitations of tractography should always be kept in mind.[1] Moreover, it appears that authors made the choice in some patients not to perform supratotal resection despite negative language and motor mapping. This is disputable, as it is expected that pushing the resection beyond the MRI-defined tumor margins could contribute to delay the recurrence and improve survival of DLGG patients,[2] and maybe even so in high-grade glioma patients.[3] The functional risk associated with supratotal resections can be controlled by monitoring abilities requiring high cognitive loads – the level of which can be discussed preoperatively with the patient – such as moving the contralateral superior limb while performing simultaneously[1] – back picture naming. In other words, some of the negative axonal mappings observed in the present series could be a consequence of stopping prematurely the resection and/or selecting intraoperative tasks with low cognitive loads.

Emmanuel Mandonnet
Paris, France

---

1. Maier-Hein KH, Neher PF, Houde J-C, et al. The challenge of mapping the human connectome based on diffusion tractography. *Nat Commun*. 2017;8(1):1349.
2. Duffau H. Long-term outcomes after supratotal resection of diffuse low-grade gliomas: a consecutive series with 11-year follow-up. *Acta Neurochir (Wien)*. 2016;158(1):51-58.
3. Zigiotto L, Annicchiarico L, Corsini F, et al. Effects of supra-total resection in neurocognitive and oncological outcome of high-grade gliomas comparing asleep and awake surgery. *J Neurooncol*. 2020;148(1):97-108.

The work presented in this manuscript further enhances the understanding of the art of resecting low-grade gliomas based on anatomical principles. The authors are to be congratulated on their excellent description of their techniques as shown by three clinical examples. As they point out in Table 2, there is a major variability concerning predictive functional values on different tracks which is an important result of this study. Such studies need further support by postoperative clinical and neuropsychological evaluation in a larger group of patients in order to further improve our technical skills.

Downloaded from https://academic.oup.com/neurosurgery/advance-article/doi/10.1093/neuros/nyaa463/6031391 by University of Western Ontario user on 21 December 2020

Somewhat disappointing it may be that even this experienced group with all technological possibilities incl. awake craniotomy achieves only about 23% of gross total resection, but, as the authors point out, new deficits significantly affect length of survival. Long-term follow-up is essential in these patients including repeat DTI studies in order to possibly show migration of the tracts and functional areas. Also, it might be interesting to speculate about the use of intraoperative high-field MRI with intraoperative tractography to further improve on the gross total resection rate while keeping neurological deficits low.

Maximilian Mehdorn
Kiel, Germany

Downloaded from https://academic.oup.com/neurosurgery/advance-article/doi/10.1093/neuros/nyaa463/6031391 by University of Western Ontario user on 21 December 2020