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Neuroanatomical Studies

The usefulness of arcuate fasciculus tractography integrated navigation for glioma surgery near the language area; Clinical Investigation

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ABSTRACT

Background: The utility of corticospinal tract (CST)-tractography-integrated navigation was reported for brain tumors near pyramidal tracts. However, the efficacy of arcuate fasciculus (AF)-tractography-integrated navigation is unclear. Awake craniotomy is recommended to preserve language function for glioma located near the language area, although the patients' condition can limit its application. In such cases, AF-tractography-integrated navigation may help protect neurological function.

Methods: We performed a retrospective analysis of AF-tractography-integrated navigation. We evaluated 11 patients who underwent glioma surgery near the language area using AF-tractography-integrated navigation. Six patients received intraoperative awake language functional mapping, whereas five did not due to adverse preoperative or intraoperative conditions. Language function was evaluated using the Western Aphasia Battery or Standard Language Test of Aphasia both preoperatively and postoperatively (2–4 weeks and 2–3 months after surgery).

Results: Extent of resection (EOR) ranged from 59.5% to 100% (mean 82.1%). Language function at 2–3 months after surgery was improved in one patient, intact in nine, and moderately disturbed in one compared with preoperative function. Among the non-awake craniotomy group, EOR ranged from 78.7% to 100% (mean 89.82%). Language function at 2–3 months after surgery was improved in one patient, intact in three, and moderately disturbed in one, in whom tumor removal very close to the AF tract was performed following preoperative patient's intent.

Conclusions: AF-tractography-integrated navigation is useful for glioma surgery near the language area, especially for patients with unsuitable conditions for awake craniotomy.

1. Introduction

In glioma surgery, the maximum extent of resection (EOR) is critical for the survival of patients [1]. Nevertheless, minimizing tissue removal for preservation of brain function is also important for their quality of life. To remove a glioma near the language area, we generally perform language mapping and monitoring under awake craniotomy to protect language function [2]. However, the patient's condition can limit the application of this technique; for example, if the patient has insufficient language potential remaining for intraoperative language evaluation, or the patient's intraoperative condition is unsuitable for intraoperative language evaluation.

Abbreviations: 3D, three-dimensional; AF, arcuate fasciculus; AQ, aphasia quotient; CCEP, Cortico-cortical evoked potential; CST, corticospinal tract; DTI, diffusion tensor imaging; EOR, extent of resection; FLAIR, fluid attenuated inversion recovery; FOV, field of view; GdT1WI, gadolinium-enhanced T1 weighted imaging; MEP, motor evoked potential; PDD, photo dynamic diagnosis; SLTA, Standard Language Test of Aphasia; TE, echo time; TI, inversion time; TR, repetition time; VOI, volume of interest; WAB, Western Aphasia Battery.

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Recently, tractography, a neural fiber bundle imaging technique derived from diffusion tensor MRI using fiber tracking technology, has been widely used to evaluate white matter connectivity. The arcuate fasciculus (AF) is considered a key associative pathway controlling verbal language function [3,4]. Several studies have reported that corticospinal tract (CST) tractography can be applied to navigation systems for operating on tumors near the motor area to protect the patient's motor functions [5–7]. As for the CST, visualization of the AF and its application to surgical navigation may be useful to protect language function during neurosurgery. However, application of AF tractography for intraoperative navigation has not been fully elucidated. Since 2012, we have used preoperative AF-tractography-integrated navigation for patients undergoing glioma surgery near the language area. In the present study, we performed a retrospective analysis of the utility of preoperative AF-tractography-integrated navigation for tumor removal.

2. Patients and methods

2.1. Patient background

Between January 2012 and June 2014, we performed surgical resection for 62 patients with gliomas (WHO grade II–IV). Among those cases, 11 patients who underwent radical glioma surgery near the language area were provided precise preoperative analysis with diffusion tensor imaging (DTI). Consequently, AF tractography was integrated into the navigation system for all patients to prevent further neurological deterioration. We obtained informed consent from each patient or next of kin in the use of AF-tractography-integrated navigation for tumor removal.

2.2. Clinical evaluation

All patients were clinically assessed by neurosurgeons and rehabilitation therapists before and after surgery. The evaluation of language function was performed using the Western Aphasia Battery (WAB) or Standard Language Test of Aphasia (SLTA), a commonly used test battery to evaluate Japanese patients with aphasia [8]. Postoperative evaluation of language was also performed at 2–4 weeks and 2–3 months after the operation.

Postoperative language function was compared with preoperative function, and was ranked as improved (improvement of aphasia quotient (AQ) in WAB, or increase in average percentage of correct answers in SLTA, by more than 3% than preoperative evaluation), intact (between 3% decline and 3% gain compared with preoperative evaluation), slightly disturbed (decline between 3% and 10% compared with preoperative evaluation), moderately disturbed (decline between 10% and 50% compared with preoperative evaluation), or severely disturbed (decline by more than 50% compared with preoperative evaluation).

2.3. Radiological data acquisition

Preoperative three-dimensional (3D) fluid attenuated inversion recovery (FLAIR), 3D gadolinium-enhanced T1 weighted imaging (GdT1WI), and DTI using a 3.0 T MRI (Philips Achieva 3.0, Philips Medical Systems, Eindhoven, the Netherlands) were performed for tumor characterization. The acquisition methods were as follows: FLAIR: scan technique = 3D fast spin-echo sequence, repetition time (TR) = 6000 ms, echo time (TE) = 270 ms, inversion time (TI) = 2200 ms, slice thickness = 1.3 mm, field of view (FOV) = 240 mm; GdT1WI: scan technique = 3D gradient-echo sequence, TR = 8.2 ms, TE = 3.8 ms, flip angle = 8°, slice thickness = 1.0 mm, FOV = 240 mm; DTI: TR = 7700 ms, TE = 90 ms, slice thickness = 2 mm, FOV = 230 mm, b value = 800 s/mm^2, motion probing gradient directions = 15. Patients also received postoperative FLAIR and GdT1 MRI as described above. Preoperative and postoperative tumor size measurement was performed by 3D volumetry. The tumor was defined as inside the GdT1WI-enhanced areas for glioblastoma, and FLAIR hyperintensity lesion for other tumors.

2.4. DTI analysis and application for the navigation system

Analysis of DTI for visualization of AF was performed using the Medtronic Stealth S7 planning station (Medtronic, Inc., Minneapolis, MN, USA). The DTI dataset and the GdT1WI or FLAIR dataset were merged automatically on the planning station. A fractional anisotropy (FA) color map was then calculated from the DTI datasets. Fiber tracking was performed as previously reported [9,10], although we modified the volume of interest (VOI) to be set on three regions, the inferior frontal gyrus (pars opercularis), the dorsolateral parietal white matter, and the superior temporal gyrus, using GdT1WI or FLAIR anatomical feature points, and the fibers crossing all of these VOI were visualized. The FA cutoff value used for AF fiber tracking was set between 0.15 and 0.2, and the maximum directional change was set between 60° and 150°. The obtained 3D AF tractography data were then superimposed onto the GdT1WI or FLAIR datasets in three planes. In some patients, tractography was also performed on the CST or optic tract (OT). Tractography superimposed images were then sent to the navigation system (Medtronic Stealth Treon; Medtronic, Inc.). Marker registration was performed and intraoperative navigation was performed.

2.5. Intraoperative use of DTI-integrated navigation system

For the awake craniotomy patients, we used the AF-tractography-integrated navigation system mainly to identify the site of direct electrical stimulation at the border of the tumor. When electrical stimulation caused any speech disturbance at the site, further tumor resection was aborted. When the electrical stimulation did not cause any speech disturbance, careful resection was continued with a continuous speech task until any sign of the speech disturbance was detected.

For the non-awake craniotomy patients, AF tractography played more important role in deciding the border of resection compared with the awake craniotomy patients. When the navigation presented AF tractography very close to the tumor removal sight, the 5-ALA system and intraoperative ultrasonography was used to detect the residual tumor. We confirmed each patient's intent before surgery to decide whether we should stop or continue removal of the tumor when residual tumor seemed very closely located to the AF tractography.

2.6. Intraoperative evaluation of language function during awake craniotomy

We performed language monitoring for awake craniotomy patients. After the patient achieved awake state, a speech therapist gave the patient language task, such as counting, reading characters, calling the things in the card, repeating small sentences, mental arithmetic, and so on during tumor resection. Surgeons sometimes gave electrical stimulation (2–10 mA, 60 Hz) to identify the language area and language pathway with 1-mm bipolar electrode separated by 5 mm. When speech arrest, anomia, alexia, or paraphasia occurred, the stimulated area was identified as a language related lesion.

3. Results

There were six males and five females, ranging from 33 to 72 years of age (mean age, 47 years). There were four grade II glioma patients, three grade III glioma patients, and four grade IV glioma patients. Tumor location was parietal (around the angular gyrus) in four patients, frontal in three patients, temporal in two patients, and insular in two patients. Two patients had anomia, one patient had fluent aphasia, one patient had alexia with agraphia, and the remaining seven patients had normal language function preoperatively (Table 1). Six patients received

Table 1
Patient's profile, location of the tumor, tumor grade, preoperative symptom, and integrated tractography for navigation.

Patient No.	Age	sex	Tumor location	WHO grade	Preoperative symptom	Tractography for navigation		
						AF	CST	OT
1	38	M	Frontal	II	Epilepsy	+	−	−
2	33	M	Parietal	II	Partial seizure	+	+	−
3	39	F	Temporal	II	Anomia	+	−	−
4	52	F	Frontal	II	Memory loss	+	−	+
5	38	M	Insular	III	Epilepsy	+	+	−
6	42	M	Parietal	III	Epilepsy	+	+	+
7	37	F	Frontal	III	Hemiparesis	+	+	−
8	38	F	Insular	IV	Dysesthesia	+	−	−
9	72	M	Temporal	IV	Anomia hemiparesis	+	+	+
10	60	F	Parietal	IV	Alexia agraphia	+	−	+
11	70	F	Parietal	IV	Fluent aphasia hemiparesis	+	+	−

Table 2
The tumor removal rate, reaction for electrical stimulation around AF, and language function after surgery in the awake craniotomy group.

Patient No.	Tumor size (ml)		Removal rate	Electrical stimulation around AF	Language function after surgery	
	Pre op.	Post op.			2–4 weeks	2–3 months
1	26	4.9	81.2	Slurred speech	Intact	Intact
2	63.2	11.6	81.6	Dysarthria	Intact	Intact
3	97.7	5.4	94.5	–	Intact	Intact
4	145.9	52.3	64.2	Speech arrest	Intact	Intact
5	115.4	46.7	59.5	Speech arrest paraphasia	Slightly disturbed	Intact
6	64.4	10.6	83.5	–	Slightly disturbed	Intact

intraoperative language area mapping by electrical stimulation in the awake condition (awake craniotomy group). On the other hand, intraoperative language area mapping was not performed in four patients as preoperative language evaluation indicated that insufficient language function remained for the intraoperative language task, and intraoperative language area mapping was stopped in one patient owing to restlessness during the task (non-awake craniotomy group).

In all patients, AF tractography tracking and integration of tractography on the navigation system was successfully performed, with a mean residual error of 0.95 mm. The final EOR ranged from 59.5% to 100% (mean, 84.3%). All patients survived after surgery over 3 months, indicating that there was no mortality directly induced by surgery. The language function at 2–4 weeks after surgery was intact in five patients, slightly disturbed in two patients, moderately disturbed in two patients, and severely disturbed in two patients compared with their preoperative language function. The language function at 2–3 months after surgery was improved in one patient, intact in nine patients, and moderately disturbed in one patient compared with their preoperative function.

In the awake craniotomy group ($n = 6$), the final EOR ranged from 59.5% to 94.5% (mean 77.4%). Electrical stimulation around AF caused some speech disturbance in four patients, and no disturbance in two patients. Language function at 2–4 weeks after surgery was intact in four patients and slightly disturbed in two patients. Language function at 2–3 months after surgery was intact in five patients and slightly disturbed in one patient (Table 2). In the non-awake craniotomy group ($n = 5$), the final EOR ranged from 78.7% to 100% (mean 89.8%). Language function at 2–4 weeks after surgery was intact in one patient, moderately disturbed in two patients, and severely disturbed in two patients. Language function at 2–3 months after surgery was improved in one patient, intact in three patients, and moderately disturbed in one patient (Table 3). Only one patient, who underwent aggressive resection of 5-ALA positive tumor, suffered persistent disturbance of language function.

The difference of preoperative tumor volume and tumor removal rate between the awake craniotomy group and the non-awake craniotomy group was not significant statistically. Two illustrative cases (Cases 8 and 11) are presented below.

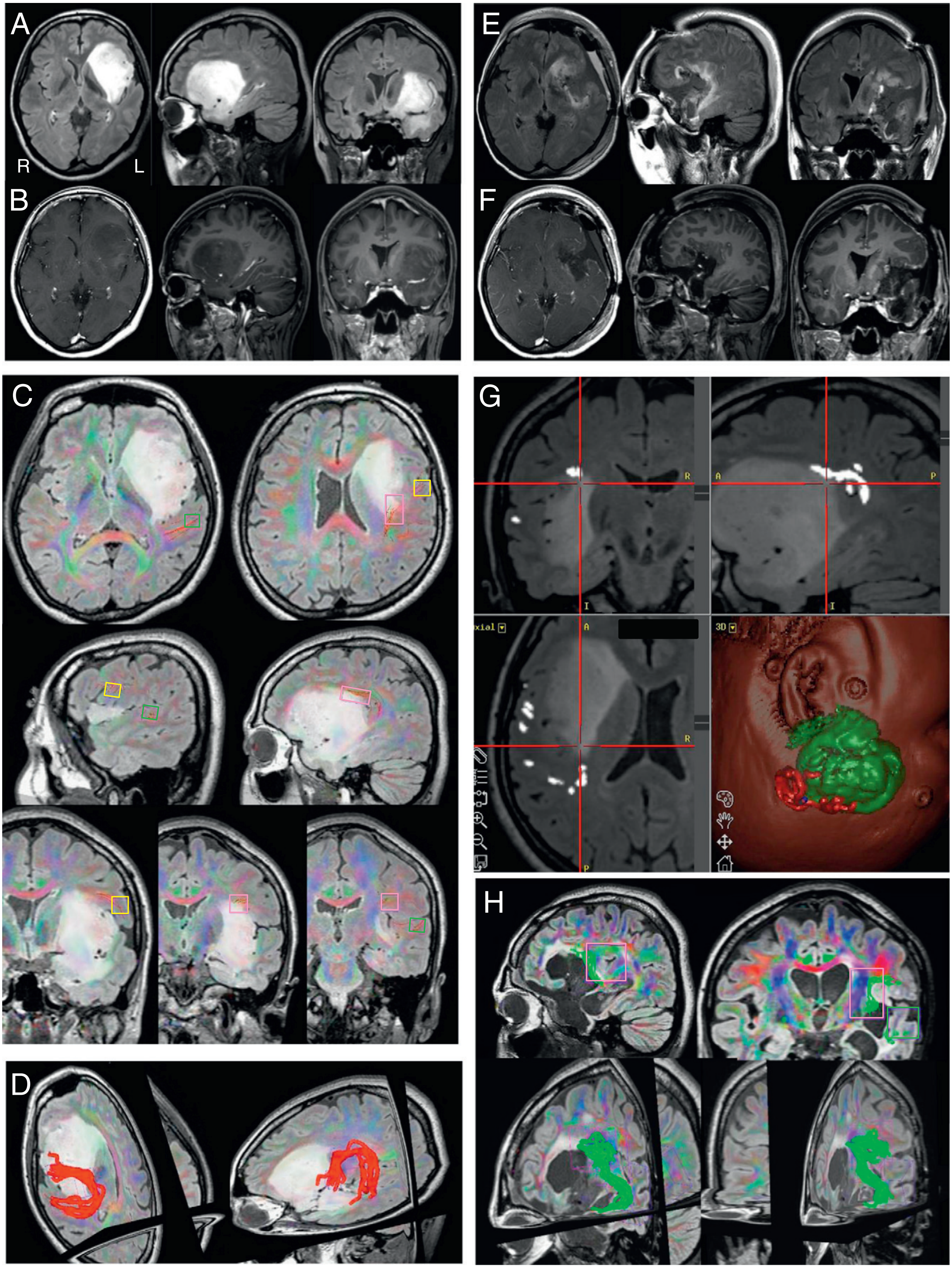
3.1. Case 8

A 38-year-old right-handed female suffered from dysesthesia in her right arm. MRI examination revealed intraaxial tumor in the left insular lesion (Fig. 1A, B). She had no abnormal symptoms with her language function. Wada test revealed her left hemisphere was dominant for language function. We planned to remove the tumor under intraoperative awake functional mapping of language and AF-tractography-integrated navigation. The AF was located adjacent to the inner-upper margin of the tumor (Fig. 1C, D). However, we decided to suspend intraoperative awake functional mapping of language as the patient became restless and would not cooperate with the task. The maximum safe resection under general anesthesia with AF-tractography-integrated navigation and transcranial motor evoked potential (MEP) was performed instead

Table 3
The tumor removal rate, language function after surgery in the non-awake craniotomy group.

Patient No.	Tumor size (ml)		Removal rate	Language function after surgery	
	Pre op.	Post op.		2–4 weeks	2–3 months
7	130	22.9	82.4	Moderately disturbed	Intact
8	75.1	16	78.7	Moderately disturbed	Intact
9	82.3	5	93.9	Severely disturbed	Improved
10	38	0	100.0	Intact	Intact
11	46.3	2.7	94.1	Severely disturbed	Moderately disturbed

Fig. 1. MRI findings, visualization of arcuate fasciculus (AF) tractography, and its application in navigation system in Case 8. (A) Preoperative fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) demonstrating a hyperintense tumor mass in the left insular lesion. (B) The tumor mass exhibits very slight contrast enhancement on gadolinium-enhanced T1 weighted images (GdT1WI). (C) The regions of interest (ROIs) are highlighted, set at the inferior frontal gyrus (Pars opercularis), dorsolateral parietal white matter, and superior temporal gyrus on fractional anisotropy (FA) color map and FLAIR fused image. (D) The obtained arcuate fasciculus (AF) tractography (red fascicle) is displayed in 3D. (E) Postoperative FLAIR image shows a slight FLAIR hyperintense lesion left at the posterior-superior portion of the tumor. (F) Postoperative GdT1W1 image shows no evidence of remaining contrast-enhanced mass. (G) Intraoperative view of AF-tractography-integrated navigation. AF tractography is displayed as a white fascicle in the 2D FLAIR image, running very close to the posterior-superior portion of the tumor. In the 3D reconstructed image, AF is displayed as a red fascicle and the tumor as a green mass. (H) AF tractography tracked on postoperative MRI. The AF tractography runs very close to the resected margin. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)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(Fig. 1G). The tumor near the arcuate fasciculus tractography was intentionally left behind.

Postoperative pathological examination revealed that the tumor was glioblastoma multiform. The tumor removal rate was 78.7%. The patient developed fluent aphasia postoperatively, and the average percentage of correct answers in the SLTA was decreased from preoperative from 96.7% to 81.3% postoperatively at 2 weeks after the operation, indicating a moderate disturbance. However, her language function rapidly improved, and the average percentage of correct answers in the SLTA at 3 months after the operation was 96.0%, unchanged from that preoperatively. In postoperative MRI, we were able to track AF tractography very close to the resected margin (Fig. 1H). The patient has survived for 2 years since surgery.

3.2. Case 11

MRI of a 70-year-old right-handed female presenting with headache and being at a loss for words revealed a gadolinium-enhanced tumor in the left parietal lobe (Fig. 2A). The result of the preoperative language functional evaluation indicated that her language function was too poor to perform intraoperative awake functional mapping of language. Preoperative arcuate fasciculus fiber tracking was successfully performed and the AF was located just adjacent to the tumors' anterior margin, in the peritumoral edema. In this case, the preoperative language function was so poor that it was not certain whether the language function would recover after tumor removal, even if the AF would be preserved.

Her family wished to remove as much tumor as possible after the preoperative informed consent. Aggressive tumor resection using AF and CST integrated navigation and neurophysiological monitoring by transcranial MEP was performed. Following the removal of the main component of the tumor and the intraoperative pathological diagnosis of GBM, additional removal using the 5-ALA PDD was performed. The navigation system indicated that the AF passed very close to the anterior margin of the tumor. However, PDD with 5-ALA indicated a large amount of tumor left at the site (Fig. 2B, C). The careful removal of the 5-ALA positive tumor was continued to get maximum tumor resection according to preoperative patient's intent. The final EOR was achieved up to 94.1% (Fig. 2D). Unfortunately, the patient's fluent aphasia worsened at 3 weeks after the operation, and was not fully recovered at 3 months.

4. Discussion

4.1. AF tractography images for glioma surgery in reported cases

Our data suggest that AF-tractography-integrated navigation may be useful when operating on tumors near the language area. To date, several studies have evaluated the contribution of intraoperative DTI-based CST for brain tumor surgery. However, there is limited evidence for use of AF tractography imaging for glioma surgery. Romano et al. [11] reported the application of AF tractography images on a navigation system to study various types of tractography (CST, AF, and OT), although they did not examine language function and AF tractography for the removal of the tumors near the language area. Kuhnt et al. [12] evaluated 32 cases of neuroepithelial tumor near the language area using DTI-tracked language pathways integrated on a navigation system. In that study, despite no neurophysiological monitoring, only one patient had a persistent language deficit postoperatively. Zhao et al. [13] reported 22 cases with AF involved glioma who underwent surgery using AF-tractography-integrated navigation with intraoperative update by 1.5 T MRI. Although awake functional mapping of language was not obtained intraoperatively, they achieved an excellent outcome of the patient's language functions. Vassal et al. [14] also reported 10 cases using AF-tractography-integrated navigation for tumor removal near the language area. In the present study, all patients received direct cortical and subcortical electrical stimulation with awake craniotomy, which induced phonemic paraphasias in five patients. These studies and our current 11 cases provide strong support for the contribution of AF tractography supported navigation in glioma surgery near the language area.

4.2. The strength of AF-tractography-integrated navigation in the present study

Our data also suggest that the AF-tractography-integrated navigation system is useful for patients who are unable to receive awake functional mapping of language due to their preoperative or intraoperative condition. With respect to glioma surgery, complete resection is generally required, especially for grade IV glioma patients, because higher EOR may leads to longer survival. However, Muragaki et al. [15] reported that leaving the residual lesion within functional eloquent brain structures can help to maintain brain function. Gulati et al. [16] also reported that surgical acquired deficits after primary resection of glioblastoma leads to a reduced likelihood of receiving adjuvant therapy. Considering these reports, even malignant glioma near the functional area should be removed with maximal attention to intraoperative functional mapping. Based on this idea, there are some reported cases that grade IV glioma was resected under awake craniotomy to preserve language function [17,18].

If the patient is not suitable for language mapping, methods for identifying the language area and language fasciculus are very limited. One method involves preoperative functional MRI under a language task. This method is useful in patients with normal language function, but has a low image resolution, low reliability in language malfunctioned patients, and it is difficult to locate the white matter fasciculus. Cortico-cortical evoked potential (CCEP) monitoring is also promising [19,20]. CCEP monitors electrical connectivity between the frontal and temporal language areas, and can be performed without a language task. However, the position of the language fasciculus in the white matter cannot be determined with CCEP alone. Placement of chronic subdural electrodes to the surgical site is another useful technique [21]. After electrode placement, cortical mapping of the language area with cortical stimulation while awake can be performed. However, this strategy requires a second operation, which has a potential for infection. There is also a possibility that the electric current may distribute wider area than the electrode placed area by cerebrospinal fluid. In addition, the white matter language pathway cannot be detected with this method. The use of AF tractography derived from DTI fiber tracking does not require a language task to display the probable language function pathway. Thus, the application of AF image to intraoperative navigation systems is a feasible method for displaying the possible language areas and white matter language fasciculus independent of the patient's conditions.

In support of our findings, Kuhnt et al. also showed good language function after tumor removal with language pathway tracts integrated on navigation, but without awake language mapping [12]. However, we suggest that tractography supported navigation alone is insufficient. Our 11 cases show that the postoperative language function of the non-awake craniotomy group was slightly improved in the awake craniotomy group than the non-awake group, though this was not statistically significant because of small patient numbers. At present, the gold standard for glioma surgery near the language area is considered to be an awake craniotomy with language mapping, while AF-tractography-integrated navigation is a support method in cases where awake craniotomy fails.

4.3. The EOR for glioma in our study

The EOR in the awake group and non-awake craniotomy group were 77.4% and 89.8%, which was not significantly different statistically in our study, but the EOR in the non-awake craniotomy group seems to be somewhat higher. This result may be brought out from our preference

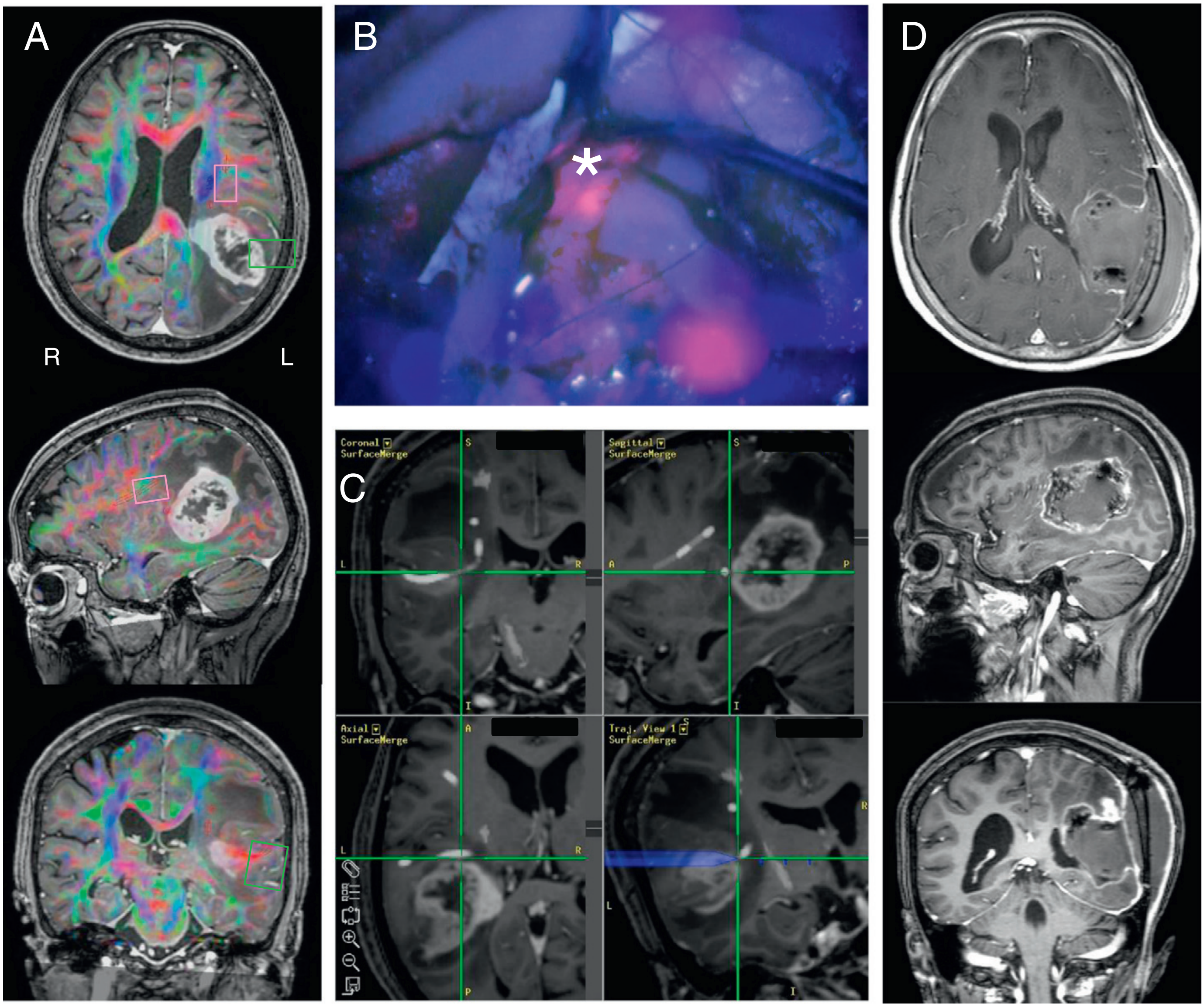

Fig. 2. MRI findings, visualization of AF tractography, its application in the navigation system, and intraoperative view in Case 11. (A) FA color map and GdT1WI-fused image indicate that the Gd-enhanced tumor is located at the parietal lobe at the angular gyrus area. The ROI for AF visualization is highlighted, set at the inferior frontal gyrus (Pars opercularis), dorsolateral parietal white matter, and superior temporal gyrus. (B) Intraoperative photodynamic diagnosis with 5-aminolevulinic acid (5-ALA) shows strong red fluorescence at the anterior-inner portion of the tumor (asterisk). (C) Intraoperative AF-tractography-integrated navigation (asterisk point, panel B) at a close localization to the tumor. (D) Postoperative GdT1WI shows successful removal of the Gd-enhanced tumor, but also slight removal over the anterior-enhanced tumor edge. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

for more aggressive tumor resection in non-awake craniotomy group because the group includes many grade IV glioma patients.

However, we don't think we should always perform complete tumor resection for grade IV glioma despite the tumor contains eloquent area or tumor is locating adjacent to eloquent area. The balance of EOR and preserving the brain function is also very important for grade IV glioma same as low grade glioma. AF tractography integrated navigation system could help to minimize language damage especially for the patients undergoing aggressive surgery under general anesthesia.

4.4. Limitations of this study

There are some limitations in our study. First, the number of patients was very small. Thus, the efficacy of the AF-tractography-integrated navigation system remains unclear. Further studies are required with a larger number of patients. Second, AF tractography images only represent a 'probable' pathway of language function. We again emphasize that intraoperative cortical and subcortical electrical stimulation is more reliable for detecting the language area and language pathway than AF tractography imaging. Therefore, awake language mapping is preferable if the patients' condition is suitable. However, our study indicates that AF tractography imaging is practically useful, especially for unsuitable patients for awake craniotomy. As presented in case 7, we aborted tumor removal near the AF, and language function 3 months after the operation was favorable. By contrast, in Case 11 (GBM case), aggressive tumor removal very close to the probable AF may have caused the worse postoperative language function. Thus, the reliability of AF tractography imaging in indicating the probable pathway of language function is high.

A further potential limitation is the existence of more complex language pathways which were not integrated to navigation system in our study. Not only Broca's area, Wernicke area and AF, multiple cortical areas and networks are associated with language function. Recently, the inferior frontooccipital fasciculus (IFOF), inferior longitudinal fasciculus

(ILF), and uncinate fasciculus (UF) were reported to be associated with language function [22–24]. Further, the connection between the supplementary motor area and Broca's area, termed the frontal aslant tract (FAT), is strongly associated with speech fluency [25]. In this study, we did not apply these tracts for navigation. Additional use of these tracts may provide further benefits for preserving language function than AF tractography alone. Finally, brain shift should always be considered when using the intraoperative navigation system for brain tumor surgery. Brain shift can be assessed using intraoperative MRI, although we do not have access to this device at present.

5. Conclusions

AF-tractography-integrated navigation for glioma surgery near the language area can help surgeons to decide the extent of the tumor resection, especially when patients are unsuitable for intraoperative awake language mapping. However, further studies with a larger population are required to evaluate true utility of AF-tractography-integrated navigation.

Disclosure

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. All patients or their next of kin has consented for submission of this article for the journal.

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