Arcuate fasciculus tractography integrated into Gamma Knife surgery

Clinical article

KEISUKE MARUYAMA, M.D., PH.D.,1 TOMOYUKI KOGA, M.D.,1 KYOUSUKE KAMADA, M.D., PH.D.,1 TAKAHIRO OTA, M.D.,1 DAISUKE ITOH, M.D., PH.D.,2 KENJI INO, R.T.,2 HIROSHI IGAKI, M.D., PH.D.,2 SHIGEKI AOKI, M.D., PH.D.,2 YOSHIKAZU MASUTANI, PH.D.,2 MASAHIRO SHIN, M.D., PH.D.,1 AND NOBUITO SAITO, M.D., PH.D.1

Departments of 1Neurosurgery and 2Radiology, The University of Tokyo Hospital, Tokyo, Japan

Object. To prevent speech disturbances after Gamma Knife surgery (GKS), the authors integrated arcuate fasciculus (AF) tractography based on diffusion tensor (DT) MR imaging into treatment planning for GKS.

Methods. Arcuate fasciculus tractography was retrospectively integrated into planning that had been previously performed by neurosurgeons and radiation oncologists. This technique was retrospectively applied to 12 patients with arteriovenous malformations adjacent to the AF. Diffusion tensor images were acquired before the frame was affixed to the patient’s head and DT tractography images of the AF were created using the authors’ original software. The data from DT tractography and stereotactic 3D imaging studies obtained after frame fixation were transported to a treatment planning workstation for GKS and coregistered so that the delivered doses and incidence of posttreatment aphasia could be assessed.

Results. The AF could not be depicted in 2 patients who initially presented with motor aphasia caused by hemorrhaging from arteriovenous malformations. During the median follow-up period of 29 months after GKS, aphasia developed in 2 patients: 30 Gy delivered to the frontal portion of the AF caused conduction aphasia in 1 patient, and 9.6 Gy to the temporal portion led to motor aphasia in the other. Speech dysfunction was not observed after a maximum radiation dose of 10.0–16.8 Gy was delivered to the frontal fibers in 4 patients, and 3.6–5.2 Gy to the temporal fibers in 3.

Conclusions. The authors found that administration of a 10-Gy radiation dose during GKS was tolerated in the frontal but not the temporal fibers of the AF. The authors recommend confirmation of the dose by integration of AF tractography with GKS, especially in lesions located near the temporal language fibers.

(DOI: 10.3171/2008.4.17521)

Key Words • arcuate fasciculus • diffusion tensor imaging • Gamma Knife surgery • treatment planning

STEREOTACTIC radiosurgery is recognized as an extremely effective treatment modality for vascular, neoplastic, or functional disorders of the brain. However, radiation-induced neuropathy occurs in 5–20% of patients and can occasionally be disabling, particularly after treatment of lesions in critical locations. Although the majority of such complications are due to parenchymal brain injury, there has been no definitive method to prevent it. To help minimize such risks, we developed a novel technique of integrating tractography based on DT MR imaging into treatment planning for GKS. By integrating tractography of the pyramidal tract and optic radiation, we have introduced an effective tool for analyzing the effect of GKS on motor and visual function. We hope that this technique will become applicable in the planning of GKS treatment. To our knowledge, there are no other reports of the application of this technique.

The AF connects the frontal and temporal language cortices and a clinically important white matter fiber tract that is only visible with the use of DT tractography. Speech disturbances were observed in 2% of patients after radiosurgery, thus the preservation of speech function is a consideration. The tolerated dose of radiation to the AF is unknown, and no definitive method of reducing the risk of these complications has heretofore been available. In the present study we report on our results with the integration of AF tractography into treatment planning for GKS.

Methods

Arcuate fasciculus tractography was retrospectively integrated into planning that had been previously per-
Arcuate fasciculus tractography in GKS

formed by neurosurgeons and radiation oncologists for GKS in 12 right-handed patients who had been treated for cerebral AVMs located adjacent to the left AF (Table I). Patients who suffered aphasia after GKS were intentionally selected to enhance the reliability of the dose-response relationship analysis. Written informed consent was obtained from all the patients. All MR imaging studies were performed with a 1.5-T whole-body MR imaging unit with echo planar capabilities and a standard whole-head transmitter–receiver coil (Signa Echospeed, General Electric).

Diffusion Tensor Imaging

Diffusion tensor MR imaging was performed without frame fixation on the day before GKS. In cases in which DT imaging had not been performed, posttreatment images were used instead. We used a single-shot, spin echo-echo planar sequence (TR 6000 msec, TE 78 msec), acquiring 32 interleaved, contiguous 2.5-mm-thick axial images with no cardiac triggering. A data matrix of $128 \times 128$ pixels over a field of view of $240 \times 240$ mm was obtained, with 128 echoes acquired per excitation. Diffusion gradients were applied in 13 noncollinear independent axes by using a b value of 0 and 1000 seconds/mm$^2$. Each echo planar imaging data set required 2 minutes and 48 seconds to obtain and was repeated twice to increase the signal-to-noise ratio. Realignment of the 13 sets of DT images and compensation for the eddy current–induced morphing were performed on the basis of the T2-weighted echo planar imaging set ($b = 0$) on an equipped workstation connected to the MR imaging unit.

Diffusion Tensor Tractography

Data sets of the realigned DT imaging and the stereotactic imaging studies were transferred to a personal computer equipped with the freely shared software programs Volume-One (Volume-One Developers Group, version 1.72; www.volume-one.org) and dTV (Yoshitaka Masutani, version II; www.ut-radiology.umin.jp/people/masutani/dTV.htm). These programs were used to calculate the DT in each voxel and create DT tractography images. The DT at each pixel of the registered DT imaging data was calculated, and 3D fiber tracking was performed using the freely shared programs. Nine ($3 \times 3 \times 3$) elements of the symmetrical DT at each voxel were determined by the least-square fit, based on singular value decomposition, and diagonalized to obtain 3 eigenvalues and 3 eigenvectors. An eigenvector associated with the largest eigenvalue was assumed to represent the local fiber orientation. Anisotropy maps were obtained using orientation-independent fractional anisotropy.

Fiber tracking was started from a manually selected start point (a “seed area”) from which lines were propagated in both the anterograde and retrograde directions according to an eigenvector at each voxel. The seed area for the AF was selected manually in the deep white matter of the posterior parietal portion of the superior longitudinal fascicle, as described previously. A target area was used to limit displayed tracking results to the AF only. The target area was drawn in freehand and encompassed the entire descending portion of the superior longitudinal fascicle in the posterior temporal lobe. Tracking was terminated when a voxel with a fractional anisotropy value of $< 0.18$ was reached.

After fiber tracking of the AF, only the voxels through which tracts ran were marked and color coded, depending on the fractional anisotropy value of each voxel. The marked voxels of the AF and the T2-weighted echo planar imaging data set were then simply fused and were reformatted using the DICOM format according to the header information on the T2-weighted echo planar imaging studies.

Stereotactic 3D Imaging

On the day of GKS, the patient was immobilized in a Leksell stereotactic coordinate frame and for stereotactic 3D anatomical MR imaging. The MR imaging study consisted of 128 sequential, 1.5-mm-thick axial slices with a resolution of $256 \times 256$ pixels over a field of view of $240$ mm with 3D spoiled-gradient recalled-acquisition in the steady-state sequence. Stereotactic angiography was also performed separately.

Image Integration and Treatment Planning

The T2-weighted echo planar imaging data with tract information, stereotactic imaging data, and the data from stereotactic angiography were transferred via fast ethernet into a treatment planning software, GammaPlan (Elekta Instruments). The T2-weighted echo planar imaging data with tract information and stereotactic imaging data were automatically coregistered by Multiview (Elekta Instruments), a supplementary software to GammaPlan for Gamma Knife 4C. The AF images were black-and-white in the DICOM format and were displayed in orange with GammaPlan to facilitate clear identification. Arcuate fasciculus tractography was thus retrospectively integrated into planning that had been previously performed by neurosurgeons and radiation oncologists. The prescribed dose to the AVM margin had been designed to be $\geq 20$ Gy by using 40–50% isodose lines.

Speech function was assessed in all patients before treatment and during the serial clinical follow-up examinations at 6-month intervals after GKS. Any patient who reported a change in speech function underwent a detailed speech function examination. The classification of aphasia was made based on standard diagnostic approaches. The relationship between the maximum dose delivered to the AF and speech dysfunction was retrospectively reviewed. To analyze the influence of low-dose volumes, we also calculated the volume of AF that received $\geq 8$ Gy.

Results

Because of DT imaging characteristics, visualizing the AF was generally more difficult than visualizing the pyramidal tract, and the volume of the AF tended to be smaller than that of the pyramidal tract. In 2 patients, data from DT MR imaging studies obtained after GKS were substituted because DT imaging had not been performed prior to GKS. When the depicted AF was divided length-
The fiber location primarily affected by the lesion was the frontal white matter in 8 patients and the temporal in 4. The AF could not be visualized in 2 patients who presented with motor aphasia caused by hemorrhaging from AVMs located in the frontal lobe and the putamen, respectively. Patients were followed up for 17–52 months (median 29 months). Two patients suffered a hemorrhage during the latency period until obliteration, but the hemorrhage did not affect speech functioning in either patient. Serial T2-weighted images showed transient or permanent perilesional edema in 3 of 12 patients. One of these patients remained asymptomatic throughout the clinical course of 28 months, but the other 2 developed speech dysfunction after GKS; these patients are described below.

Speech Dysfunction After GKS

A 48-year-old man who underwent GKS for a ruptured parietal AVM developed a speech disturbance 1 month postoperatively. He had received a 20-Gy radiation dose to the margin. A detailed examination revealed literal paraphasia, moderately impaired verbal fluency, poor repetition, and normal comprehension. His symptoms were considered to indicate conduction aphasia.2,8,11 Neuroimaging studies demonstrated a mild adverse radiation effect in the parietal paraventricular territory surrounding the AVM nidus (Fig. 1). The conduction aphasia gradually improved, and he recovered fully over a clinical course of 4 months. According to our retrospective analysis, the frontal portion of the AF had been irradiated with 30.0 Gy at a maximum, and the dose to the language cortex was 2.9 Gy in the Broca area and 0.6 Gy in the Wernicke area.

The other patient in whom speech dysfunction arose was a 45-year-old man with an unruptured temporal AVM. Wada testing performed before GKS confirmed the left side to be his dominant hemisphere. Ten months after a dose of 20 Gy had been administered to the AVM margin, this patient began to experience speech and handwriting difficulties. Naming was poor but comprehension was intact and his symptoms were considered Broca aphasia.2,8,11 Neuroimaging studies demonstrated a severe adverse radiation effect in the wide subcortical area around the left temporal AVM (Fig. 2). The aphasia gradually improved, and the patient fully recovered over a clinical course of 9 months. Our retrospective analysis indicated that the maximum dose to the temporal portion of the AF was 9.6 Gy. The dose to the language cortex was 2.7 Gy in the Broca area, and 3.6 Gy in the Wernicke area. In both patients with postoperative speech dysfunction, 20 Gy was delivered to a volume > 10 cm³.

The remaining 8 patients did not show speech disturbances during the clinical course (Fig. 3). The maximum dose to the AF was 10.0–16.8 Gy to the frontal fiber in 4 patients and 3.6–5.2 Gy to the temporal fibers in 3. A high dose of ≥ 20 Gy was delivered to an 11.2 cm³ volume in a patient who received 17 Gy to 18.9 cm³. Of 8 patients who did not experience dysphasia, 20 Gy was delivered to a volume of > 10 cm³ in 2. As the volume of the AF that received ≥ 8 Gy increased, the maximum dose to the AF tended to increase. No patient suffered speech disturbances after receiving a relatively low dose of radiation to a large volume (Table 1). Logistic regression analysis was performed to analyze the relationship of the maximum dose to the AF and speech dysfunction, but no significant correlation was found.

### Discussion

In our experience with this limited cohort, aphasia was observed after irradiation of 9.6 Gy to the temporal fibers and 30 Gy to the frontal fibers of the AF, but
Arcuate fasciculus tractography in GKS

Fig. 1. Axial (A), coronal (B), 3D reconstruction image (C), and sagittal (D) radiosurgical dosimetry studies on T2-weighted MR images showing the results of integrating the AF tractography (with the AF shown in orange) in a 48-year-old man who developed conduction aphasia 1 month after GKS. The maximum dose to the AF was 30.0 Gy. The spatial relationship between the dose distribution and the AF is clearly demonstrated in the 3D MR reconstruction. The yellow object in C represents the volume that received 20 Gy. The green and light blue mesh correspond to the volumes that received 10 and 5 Gy, respectively. Comparison of image obtained before GKS (E) with that obtained 1 month postoperatively (F) demonstrates a mild adverse radiation effect.

Fig. 2. Axial (A), coronal (B), 3D reconstruction image (C), and sagittal (D) radiosurgical dosimetry studies on T2-weighted MR images showing the results of AF tractography integration with GKS planning in a 45-year-old man who developed Broca aphasia 10 months postoperatively. The maximum dose to the AF was 9.6 Gy. In the 3D reconstruction (C), the yellow object represents the volume that received 20 Gy. The green and light blue mesh correspond to the volumes that received 10 and 5 Gy, respectively. Comparison of the image obtained before GKS (E) with that obtained 10 months postoperatively (F) demonstrates a severe adverse radiation effect.
Thus, it seems that the threshold of AF radiation tolerance differs between the frontal and temporal fibers. That is, tolerance to GKS was suggested to be lower in the temporal fibers than in the frontal fibers. According to reports on the cranial nerves, tolerance to radiosurgery is lower in the sensory nerves than the motor nerves, and the results of this study were consistent with these findings when the sensory nerves are regarded as the input fibers and the motor nerves as the output fibers. Additionally, it is interesting to note that the dose threshold of the frontal and temporal portions of the AF was almost similar to that of the optic radiation (input fibers) and the pyramidal tract (output fibers), respectively. The dose-complication relationship was not correlated to the logistic regression curves, and the dose threshold was not calculated for the AF. This might be because the number of patients suffering from aphasia was small. Although definitive conclusions on radiation tolerance cannot be drawn from our limited experience, no other institutes have reported a similar effort and this technique is possible only at our institution. Our study results will undoubtedly provide fundamental data that can be used in future studies concerning the tolerance of the frontotemporal language fibers to radiation. The follow-up in our patients is also relatively limited, and the long-term consequences of radiation to this white matter tract remain unknown. More detailed information on radiation tolerance must be clarified by further advances in neuroimaging techniques and the accumulation of data in more patients with a longer follow-up.

Because the dose to the language cortices was sufficiently low in 2 patients who suffered speech dysfunction, aphasia could be attributable to a direct radiation injury to the AF. As 1 patient developed aphasia 1 month after GKS for radiation injury, other kinds of complications such as seizures could be part of the differential diagnosis. However, adverse radiation effects were confirmed on neuroimaging studies and the 4-month recovery period was compatible with radiation injury, although a definitive diagnosis could not be rendered without obtaining a surgical specimen. In the 2 patients who suffered aphasia, 20 Gy was applied to a volume of > 10 cm³. Because a high dose was delivered to a wide area of the AF, the high radiation dose could be related to aphasia. Remarkably, injury to the frontal fibers resulted in conduction aphasia, a typical symptom of damaging the AF, while injury of the temporal fibers did not lead instead to motor aphasia, a condition for which no formal speech function examination is performed. The reasons for this finding remain speculative; the semantic system is composed of more complex connecting and associating fibers than the...
simple input or output fibers, such as the optic radiation or the pyramidal tract. An injury to the AF fibers might not necessarily cause language dysfunction because language processing requires the participation of a distributed neural system in the left hemisphere.4,26

There exist several limitations in the AF tractography. The AF could not be visualized in 2 patients who presented with aphasia before treatment, which was consistent with findings in a previous report.3 In general, DT tractography is not suitable for describing bending or crossing fibers such as the AF or the optic radiation.22 Narrowing of the AF in the presence of an AVM has also been examined both qualitatively5,6 and quantitatively,22 and the existence of several branching of the AF.4 Additionally, the extent of depicting the AF depends on language dominance.21,27

Thus, it is possible that only part of the AF could be visualized. Another issue is whether the depicted tracts represent true language fibers. To solve these problems, AF tractography was validated with intraoperative electrical stimulation during awake surgery at our institute.7 The addition of functional MR imaging or magnetoencephalography studies conducted before treatment would enhance the reliability of preoperative AF localization and enable appropriate selection of the seed and target points.7

By a series of clinical simulation studies including this one, we have integrated tractography studies into GKS dosimetry plots.13–15 We expect that this technique will be applied in the wide variety of stereotactic radiosurgical procedures including linear accelerator radiosurgery, and we hope that the safety of stereotactic radiosurgery will be improved as a result.

Conclusions

In our experience with a limited cohort, the administration of 10 Gy during GKS was tolerated in the frontal but not in the temporal fibers of the AF. Based on this observation, confirmation of the dose to be delivered by integrating AF tractography into GKS is recommended, especially in lesions located adjacent to the temporal language fibers.

Disclosure

This work was supported in part by Takeda Science Foundation and grants-in-aid for scientific research awarded to Dr. Maruyama from the Ministry of Education, Science, and Culture of Japan (Grant No. 18791013).

References


Accepted April 14, 2008.
Please include this information when citing this paper: published online November 21, 2008; DOI: 10.3171/2008.4.17521.
Address correspondence to: Keisuke Maruyama, M.D., Ph.D., Department of Neurosurgery, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. email: kskmaru-ty@umin.ac.jp.