Integration of three-dimensional corticospinal tractography into treatment planning for gamma knife surgery

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Object. In the radiosurgical treatment of critically located lesions, the effort to minimize the risk of complication is essential. In this study the integration of diffusion-tensor (DT) imaging–based tractography was clinically applied to treatment planning for gamma knife surgery (GKS).

Methods. Seven patients with cerebral arteriovenous malformations located adjacent to the corticospinal tract (CST) underwent this technique. Data provided by DT imaging were acquired before the frame was affixed to the patient’s head and the CST of the DT tractography was created using our original software. Stereotactic three-dimensional imaging studies were obtained after frame fixation and then coregistered with the data from DT tractography. After image fusion of the two studies, the combined images were transported to a GKS treatment-planning workstation. The spatial relationship between the dose distribution and the CST was clearly demonstrated within the 2 hours it took to complete the entire imaging process. The univariate logistic regression analysis of transient or permanent motor complications revealed a significant independent correlation with the volume of the CST that received 25 GY or more and with a maximum dose to the CST (p < 0.05).

Conclusions. The integration of DT tractography into the GKS treatment planning was highly useful in confirming the dose to the CST during treatment planning.

Key Words • corticospinal tract • diffusion-tensor imaging • gamma knife surgery • magnetic resonance imaging • stereotactic radiosurgery • treatment planning

Gamma knife surgery has been widely recognized and used as a safe and effective treatment modality for various intracranial lesions during the past two decades. Because of its noninvasive nature, this procedure is considered one of the most suitable modalities to treat critically located lesions that are not easily accessible when using neurosurgical approaches. Despite the benefits of radiosurgery, radiation-induced neuropathy, caused by excessive irradiation, is still a major concern for some patients. In treating critically located lesions, therefore, the strenuous endeavor has been made to diminish the risk of its complications.

With the aid of contemporary neuroimaging techniques, many critical intracranial structures such as cranial nerves can be well demarcated on imaging studies. In radiosurgical treatment, the dose of radiation delivered to these structures can be easily modified by taking into consideration the known tolerable radiation dose so as to avoid the possible risk of neurological deterioration. Despite recent advances in neuroimaging, however, fiber connections in the white matter of the brain, including the CST, are difficult to trace accurately on routine neuroimaging studies. Thus, there has been no way to avoid excessive irradiation of white matter fiber tracts and, consequently, the radiation doses these fiber connections can tolerate are still unknown.

Recently, we succeeded in visualizing fiber tracts in the white matter of the brain by integrating MR DT imaging studies and realized its clinical application. This technique was also applied to GKS treatment planning. In this article we introduce this novel technique and elucidate the results of its initial clinical application.

Clinical Material and Methods

Visualization of the CST was retrospectively performed in seven patients who had previously undergone GKS for cerebral AVMs located adjacent to the CST (Table 1). All MR imaging studies were performed with the aid of a 1.5-tesla whole-body MR imaging unit with echo planar capabilities and a standard whole-head transmitter–receiver coil (Signa Echospeed; General Electric, Southfield, WI).

Diffusion-Tensor Imaging Study

Diffusion-weighted imaging was performed without frame fixation on the day before radiosurgery. We used a single-shot spin echo–echo planar sequence (TR 6000 msec, TE 78 msec), acquiring 32 interleaved contiguous 5-mm-thick axial images with no cardiac triggering. A data

Abbreviations used in this paper: AVM = arteriovenous malformation; CST = corticospinal tract; CT = computerized tomography; DICOM = Digital Imaging and Communications in Medicine; DT = diffusion tensor; FA = fractional anisotropy; GKS = gamma knife surgery; MR = magnetic resonance; 3D = three-dimensional.
After the registration of 128 × 128 over a field of view of 240 × 240 mm was obtained, acquiring 128 echoes per excitation. Diffusion gradients were applied in 13 noncollinear independent axes by using a b value of 0 and 1000 seconds/mm². A single echo planar imaging set took 2 minutes and 48 seconds and was repeated twice to increase the signal-to-noise ratio. Realignment of the 13 sets of DT imaging images and compensation for the eddy current–induced morphing were performed on the basis of the T₁-weighted echo planar imaging set (b = 0) on an equipped workstation that used the MR imaging unit.

**Stereotactic 3D Imaging Study**

On the day of radiosurgery, the patient was immobilized in a Leksell stereotactic coordinate frame and underwent stereotactic 3D anatomical MR or CT imaging. The MR imaging study consisted of 128 sequential, 1.5-mm-thick axial slices with a resolution of 256 × 256 pixels over a field of view of 240 mm with 3D spoiled gradient–recalled acquisition in the steady state sequence. The CT scanning study consisted of 1-mm-thick axial slices with a resolution of 512 × 512 pixels.

**Image Registration**

The realigned DT imaging data sets and the stereotactic imaging studies were transferred to a personal computer equipped with the freely shared programs Volume-One (version 1.56) and dTV (version II). These programs, which are available online at www.volume-one.org and www.ut-radiology.umin.jp/people/masutani/dTV.htm, respectively, calculated the DT in each voxel and created the DT tractography image. Thirteen DT imaging sets and stereotactic imaging studies were independently stored, and an automatic coregistration by affine transformation between the T₁-weighted echo planar imaging set and the stereotactic imaging studies was performed based on maximizing the mutual information of these two data sets. After the registration process, the results were visually evaluated by at least two neuroradiologists and one neurosurgeon.

**Diffusion-Tensor Tractography**

After image registration, the DT at each pixel of the registered DT imaging data was calculated and 3D fiber tracking was performed using the freely shared programs. Six elements of the symmetrical DT at each voxel were determined by the least-square fit, based on single value decomposition, and diagonalized to obtain three eigenvalues and three eigenvectors. An eigenvector (e1) associated with the largest eigenvalue (λ1) was assumed to represent the local fiber direction. Anisotropy maps were obtained using orientation-independent FA.

Fiber tracking was initiated from a manually selected seed area from which lines were propagated in both antegrade and retrograde directions according to e1 at each pixel. Because we were interested in drawing only the CST in this study, the seed area was placed on the cerebral peduncle, through which only descending fibers run. Cortical target regions were carefully placed in the suspected primary motor cortex. In this study, we used the two-regions-of-interest method (involving the seed and target regions) to visualize only the descending fiber from the primary motor cortex to the cerebral peduncle. Tracking was terminated when it reached a pixel with an FA lower than 0.18.

After creating the CST, only voxels through which tracts run were marked and color coded, depending on the FA value in each voxel (voxelization). The marked voxels of the CST and stereotactic imaging studies were then simply fused and resliced using the DICOM format according to the header information on the original stereotactic imaging studies.

**Image Integration and Treatment Planning**

Resliced stereotactic imaging studies with tract information and stereotactic angiography, which was performed separately with the aid of frame fixation, were transferred via fast ethernet to a computer workstation running a treatment-planning software program (GammaPlan; Elekta Instruments, Norcross, GA). The CST, which appeared as black-and-white images in the DICOM format, was displayed as orange by using software to facilitate clear identification during the treatment planning. The planning had been performed both by neurosurgeons and radiation oncologists. The prescribed dose to the AVM margin had been designed to be 20 Gy or greater by using 50% isodose lines. To analyze the relationship between these volumes and the subsequent development of a complication, volumes of the CST receiving no less than 20 Gy, 25 Gy, and a maximum dose to the CST were calculated in each patient by using GammaPlan software. By using these values, the univariate logistic regression analysis was performed to produce dose–response curves.
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Results

The CST was clearly visualized on the GammaPlan after the introduction of DT tractography in all seven patients (Fig. 1), although its exact location, especially in deep white matter, could not be identified using conventional sequences such as enhanced CT or T1-weighted MR imaging studies. The time required to obtain the images was approximately 10 minutes; it took approximately 1 minute for tract reconstruction and 2 hours or less for the entire imaging processing. This duration was considered acceptable for patients in whom frame fixation was used.

Clinical follow up after radiosurgery ranged from 19 to 32 months (median 22 months). Three patients exhibited a motor complication during this period (Table 1). During treatment planning in one patient (Case 2), the location of the CST was not clear because DT tractography was not available at the time radiosurgery was performed in this patient. Therefore, its position was speculated based on its location in the contralateral internal capsule. After a retrospective review of the dosimetry was undertaken using our new technique, we were aware of a large divergence in the location of the bilateral internal capsule in this patient (Fig. 1A and B). As a result, we could not protect the CST from a high dose of radiation, which caused permanent hemiparesis 11 months after radiosurgery. The volume of the CST that had been irradiated with 25 Gy was 89 mm$^3$. In another patient (Case 5) who displayed mild and transient hemiparesis, a small area of the CST received 25 Gy. A 34-year-old woman in whom 25 Gy was delivered to a small area of the CST displayed no motor deficit during the follow-up period.

The univariate logistic regression analysis of transient or permanent motor complications revealed a significant independent correlation with the volume of the CST receiving 25 Gy or more and with the maximum dose to the CST ($p < 0.05$). The volume of the CST receiving 20 Gy or more did not show a significant correlation ($p = 0.064$). Sigmoid dose–response curves were generated as Fig. 2. The estimated probability ($p$) of developing transient or permanent motor complications from the logistic regression models was the following: $p = e^{\frac{A}{1 + e^{B}}}$, where $A = \text{constant} \times (\frac{-3.090}{0.054} \times (\text{volume of the CST in cubic millimeters receiving } \geq 25 \text{ Gy}), \text{ or constant} \times (\frac{-6.336}{0.230} \times (\text{maximum dose to the CST in Grays})$. According to this model, the risk of a motor complication was estimated to be 50% when 60 mm$^3$ of the visualized CST received more than 25 Gy or when the maximum dose to the CST was 28 Gy.

Discussion

We developed a method of integrating DT tractography into GKS treatment planning. Using stereotactic radiosurgery, the efficacy of controlling targeted lesions increases proportionally with the elevation of the delivered dose. On the contrary, however, the risk of radiation-induced neuropathy is also raised in association with increasing the dose. Therefore, when critical structures such as the CST are involved or closely adjacent to the treated lesions, the radiation dose to be prescribed occasionally has to be modified to decrease the risk of neurological deterioration. Before introducing this method to radiosurgical treatment planning, we had to choose whether to reduce the radiation dose to avoid excess irradiation to the ambiguously positioned CST or to deliver a sufficient dose, placing efficacy before safe-
ty. By using this new technique, we can deliver a sufficiently effective dose to targeted lesions while minimizing the risk of complications. In practice, after learning the dose tolerance, we tried to reduce the dose to within 25 Gy in any part of the visualized CST during treatment planning in some patients while delivering at least 20 Gy to the entire AVM nidus (Fig. 3).

We consider the advantage of this technique to be two-fold. First, this technique can be applied both to stereotactic MR and CT imaging studies. Currently MR imaging is more commonly used for GKS treatment planning, but produces a larger degree of distortion than CT scanning. Therefore, it is greatly advantageous that the data derived from DT imaging can be integrated into CT scans. Second, this method can be applied not only prospectively to treatment planning in a new patient, but also retrospectively to an evaluation of the previous treatment dosimetry. To use this method to evaluate the irradiated dose, as we did however, DT imaging has to have been performed before the treatment or not too late after treatment, because the subsequent decrease in the lesion volume after radiosurgery may cause a shift in the CST. Using this imaging modality, the dose delivered to the CST at the previous treatment can be accurately assessed, and may possibly be used to establish the tolerance of the CST to single-fraction irradiation.

Incorporation of other imaging modalities, such as positron emission tomography, single-photon emission computerized tomography, or MR angiography, into the GammaPlan has been previously described. Because the integration of these imaging modalities permits the development of more sophisticated and safer radiosurgical treatment, the latest treatment-planning software (GammaPlan 4C) makes it possible to incorporate color images from these studies. We hope our technique will also be applied to future treatment-planning software so that even physicians who are unfamiliar with complicated imaging processing can use our technique.

Because this method has quite recently been developed, it still holds some potential limitations. First is a potential imaging error. The DT imaging study is usually performed using single-shot echo planar imaging, but this imaging study produces a severe susceptibility artifact when a metal frame is used. Therefore, it has to be performed in advance before frame fixation. The information on the CST has to be fused with stereotactic MR or CT images obtained after frame fixation, which can potentially yield some degree of imaging error between the two imaging studies.

Another concern is whether the visualized fiber tract actually corresponds to the true anatomical CST. The visualized tract, however, is believed to represent the fiber connection between the motor cortex and the cerebral peduncle; based on our knowledge of brain anatomy, it is credible that the visualized tract corresponds to the true anatomical CST. In a clinical situation, moreover, this imaging technique is presently the only way we can visualize the CST so that we can refer to it during treatment planning. Furthermore, it is clinically meaningful to clarify the tolerable dose of the “visualized” CST instead of the true “anatomical” CST.

Conclusions

According to the analysis of the relationship between the dose delivered to the CST and the development of a complication, a dose to the CST lower than 25 Gy is ideal to avoid motor deficits. Based on this experience, the technique we describe would have a most beneficial effect when treating noninvasive benign lesions near the CST that require a maximum dose greater than 25 Gy. On the other hand, it would be questionable to propose our technique for invasive, malignant lesions such as malignant gliomas or metastatic brain tumors, in which compromised treatment directly affects prognosis. Although this method can most suitably visualize the CST as we did, most major white matter fiber connections can be visualized in theory. If this is possible, the tolerable dose of various white matter tracts in the brain can be potentially analyzed. Thus, we believe the novel technique described in this report is a highly useful
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Fig. 3. Radiosurgical dosimetry obtained in a 43-year-old woman with an AVM in the motor cortex in whom this technique was prospectively applied. The dose delivered to the CST before reference to the DT tractography (left) could be intentionally reduced after the integration of the tractography (shown in orange, center). The spatial relationship between the dose distribution and the CST was clearly demonstrated in a 3D reconstructed image (right). The yellow object represents the volume that received 20 Gy. The green area and the light blue mesh correspond to the volumes that received 10 and 5 Gy, respectively.

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