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CLINICAL INVESTIGATION **Brain**

TOLERANCE OF PYRAMIDAL TRACT TO GAMMA KNIFE RADIOSURGERY BASED ON DIFFUSION-TENSOR TRACTOGRAPHY

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Purpose: **To minimize the morbidity of radiosurgery for critically located lesions, we integrated diffusion-tensor tractography into treatment planning for gamma-knife radiosurgery. We calculated the refined tolerance of the pyramidal tract (PT) after prospective application of the technique to additional patients.**

Methods and Materials: **The relationship between the dosimetry during treatment planning and the development of subsequent motor complications was investigated in 24 patients, 9 studied retrospectively and 15 studied prospectively. The maximal dose to the PT and the volumes of the PT that received ≥20 Gy (20-Gy volume) and ≥25 Gy (25-Gy volume) were calculated. Univariate logistic regression analyses were used to produce dose–response curves. Differences in the tolerable dose according to the PT location were calculated.**

Results: **Univariate logistic regression analysis of the motor complications revealed a significant independent correlation with the maximal dose to the PT and the 20- and 25-Gy volumes. The maximal dose to the PT with a 5% risk of motor complications was 23 Gy compared with 15 Gy in our previous report. The risk of motor complications was significantly greater in the internal capsule than in the corona radiata for the 20- and 25-Gy volumes in generalized Wilcoxon tests ($p = 0.031$), although no significant difference was observed for the maximal dose.**

Conclusion: **The tolerable dose of the PT was greater than that previously reported. The internal capsule was more sensitive to high-dose irradiation over a wide area of the PT, probably owing to the dense concentration of motor fibers.** © **2008 Elsevier Inc.**

Diffusion-tensor tractography, Gamma-knife radiosurgery, Internal capsule, Pyramidal tract, Tolerance.

INTRODUCTION

Radiosurgery, including a gamma knife, is often used to treat critically located lesions that are not suitable for surgical resection (1–5). However, this approach can occasionally cause disabling complications after treatment (3, 6–8). The risk of radiation-induced deficits after radiosurgery for arteriovenous malformations located in the motor cortex region was reported to be 3% (6) and increased to 12–19% when lesions in the thalamus, basal ganglia, and brain stem were included (7–9). Thus, patients undergoing treatment for critically located lesions have previously accepted a certain risk. The development of a more sophisticated technique was desirable to minimize these complications.

To overcome this problem, we began to integrate diffusion-tensor tractography (10–13) into treatment planning for gamma-knife radiosurgery and reported on this initial clinical application in a retrospective analysis in 2005 (14). At the same time, illustrated pyramidal tractography was shown to reflect the actual pyramidal tract (PT) (11). However, the number of patients studied was limited ($n = 7$), and the results were preliminary. Subsequently, the technique was prospectively applied to additional patients, as well as those with lesions adjacent to the optic radiation (15). This made it possible to refine the dose tolerance of the PT, and to clarify the differences in the tolerable dose according to the location of the PT. We report on the refined tolerance calculated using the data from the additional patients treated at our institute.

METHODS AND MATERIALS

Diffusion-tensor tractography was integrated into treatment planning for gamma-knife radiosurgery in patients with arteriovenous malformations located adjacent to the PT (Table 1). Only those

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who were followed for ≥6 months after radiosurgery were included. The final study group contained 24 patients. Of these, the dosimetry during treatment planning was retrospectively reviewed for 9 patients, and pyramidal tractography was prospectively integrated into the treatment planning for 15 consecutive patients. For the retrospective study group, patients with motor complications were intentionally selected to improve the reliability of the dose–response relationship calculation. All patients provided written informed consent. The magnetic resonance imaging (MRI) studies were performed using a 1.5T whole-body MRI scanner with echoplaner capabilities and a standard whole-head transmit-receiver coil (Signa, Echospeed, General Electric, Southfield, WI).

Diffusion tensor imaging study

The diffusion-weighted imaging study was performed on the day before radiosurgery without frame fixation. We used a single-shot spin-echo echoplanar sequence, with a relaxation time of 6,000 ms and an echo time of 78 ms, to acquire 32 interleaved contiguous 2.5-mm-thick axial images with no cardiac triggering. A data matrix of 128 × 128 was obtained over a field of view of 240 × 240 mm, acquiring 128 echoes per excitation. Diffusion gradients were applied in 13 noncollinear independent axes, using *b*-values of 0 and 1,000 s/mm^2. Each echoplaner imaging set took 168 s to acquire and was repeated twice to increase the signal/noise ratio. Realignment of the 13 sets of diffusion-tensor images and compensation for the eddy current-induced morphing were performed on the basis of the T_2-weighted echoplaner imaging set ($b = 0$) using a workstation equipped with the MRI scanner.

Stereotactic three-dimensional imaging study

On the day of radiosurgery, each patient was immobilized in a Leksell stereotactic coordinate frame and underwent stereotactic three-dimensional anatomic MRI or computed tomography. The MRI 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 three-dimensional spoiled gradient-recalled acquisition in the steady-state sequence. The computed tomography study consisted of 1.0-mm-thick axial slices with a resolution of 512 × 512 pixels.

Image registration

The realigned diffusion-tensor imaging data sets and the stereotactic images were transferred to a personal computer equipped with the free-share programs Volume-one (version 1.72) and dTV (version II), available on-line at www.volume-one.org/ and www.ut-radiology.umin.jp/people/masutani/dTV.htm, respectively. These programs were used to calculate the diffusion tensor in each voxel and to create a diffusion-tensor tractography. In total, 13 diffusion-tensor imaging sets and stereotactic images were stored independently, and automatic co-registration by affine transformation between the T_2-weighted echoplaner imaging set and the stereotactic imaging data was performed, based on maximizing the mutual information contained within the two sets (16). After the registration process, the results were visually evaluated by at least two neuroradiologists and one neurosurgeon.

Diffusion tensor tractography

After image registration, the diffusion tensors for each pixel of the registered diffusion-tensor imaging data were calculated, and three-dimensional fiber tracking was performed using the free-share programs. Six elements of the symmetric diffusion tensor at each voxel were determined by least-square fitting based on single-value decomposition and were diagonalized to obtain three eigenvalues and three eigenvectors. The eigenvector associated with the largest eigenvalue was assumed to represent the local fiber direction. Anisotropy maps were obtained based on the orientation-independent fractional anisotropy.

Fiber tracking was initiated from a manually selected seed area, from which lines were propagated in both anterograde and retrograde directions according to the eigenvector at each pixel. Because we were interested in the PT alone in this study, the seed area was placed on the cerebral peduncle, where only descending fibers run through. The cortical target regions were carefully positioned in the suspected primary motor cortex. We used the two regions of interest method (*i.e.*, the seed and target regions) to visualize only the fiber descending from the primary motor cortex to the cerebral peduncle. The tracking was terminated when it reached a pixel with fractional anisotropy <0.18.

After fiber tracking of the PT, only the voxels through which the tracts ran were marked and color coded, depending on the fractional anisotropy value in each voxel. The marked voxels of the PT and the stereotactic imaging data were then simply fused and resliced in the Digital Imaging and Communications in Medicine (DICOM) format according to the header information of the original stereotactic imaging studies.

Image integration and treatment planning

The resliced stereotactic imaging data with tract information and stereotactic angiography, which was separately performed under frame fixation, were transferred using a fast-Ethernet connection to the GammaPlan treatment planning software (Elekta instruments, Norcross, GA). The PT, which appeared as a black-and-white image in the DICOM format, was displayed in orange using this software program to facilitate clear identification during treatment planning. The planning had been performed by both neurosurgeons and radiation oncologists. The prescribed dose at the margin of the arteriovenous malformations had been designed to be ≥20 Gy using 50% isodose lines. In the prospective study group, the PT was kept outside the 20-Gy isodose line as much as possible according to our initial experience (14), and 20 Gy was generally delivered to the margin of the lesion (Fig. 1).

Follow-up and statistical analysis

Serial clinical and imaging follow-up of the treated patients was performed every 6 months after radiosurgery. To analyze the relationship between the radiation doses and the subsequent development of complications, the volumes of the PT receiving ≥20 Gy (20-Gy volume) and ≥25 Gy (25-Gy volume) and the maximal dose to the PT were calculated for each patient using GammaPlan. These doses were selected on the basis of the findings from our previous study, in which the tolerable dose of the PT was shown to be 20–25 Gy. Univariate logistic regression analyses were used to analyze the factors potentially affecting the development of motor complications and to produce refined dose–response curves. To investigate the variation of the tolerable dose according to the main location of the involved PT, the curves were divided into those of the corona radiata and the internal capsule, and the differences were statistically analyzed using generalized Wilcoxon tests. A probability value of <0.05 was considered to indicate statistical significance.

RESULTS

The main location of the involved PT was the corona radiata in 16 patients and the internal capsule in 8 (Table 1). The target volume was 0.1–18.9 cm^3 (median, 7.0). The distance