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Corticospinal tract-sparing intensity-modulated radiotherapy treatment planning

Hiroshi Igaki[a,*], *Akira Sakumi*[a], *Akitake Mukasa*[b], *Kuniaki Saito*[b], *Akira Kunimatsu*[a], *Yoshitaka Masutani*[a], *Shunya Hanakita*[b], *Kenji Ino*[a], *Akihiro Haga*[a], *Keiichi Nakagawa*[a], *Kuni Ohtomo*[a]

[a] *Department of Radiology, The University of Tokyo Hospital, Tokyo, Japan*
[b] *Department of Neurosurgery, The University of Tokyo Hospital, Tokyo, Japan*

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ABSTRACT

Aim: To establish intensity-modulated radiotherapy (IMRT) planning procedures that spare the corticospinal tract by integrating diffusion tensor tractography into the treatment planning software.

Background: Organs at risk are generally contoured according to the outline of the organ as demonstrated by CT or MRI. But a part of the organ with specific function is difficult to protect, because such functional part of the organ cannot be delineated on CT or conventional sequence of MRI.

Methods: Diagnostic and treatment planning images of glioblastoma patients who had been treated by conventional 3-dimensional conformal radiotherapy were used for re-planning of IMRT. Three-dimensional fiber maps of the corticospinal tracts were created from the diffusion tensors obtained from the patients before the surgery, and were blended with the anatomical MR images (i.e. gadolinium-enhanced T1-weighted images or T2-weighted images). DICOM-formatted blended images were transferred and fused to the planning CT images. Then, IMRT plans were attempted.

Results: The corticospinal tracts could be contoured as organs at risk (OARs), because the blended images contained both anatomical information and fiber-tract maps. Other OARs were contoured in a way similar to that of ordinary IMRT planning. Gross tumor volumes, clinical target volumes, planning target volumes, and other OARs were contoured on the treatment planning software, and IMRT plans were made.

Conclusions: IMRT plans with diminished doses to the corticospinal tract were attained. This technique enabled us to spare specific neuron fibers as OARs which were formerly "invisible" and to reduce the probability of late morbidities.

* *Corresponding author at*: Department of Radiology, The University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Tel.: +81 3 5800 8666; fax: +81 3 5800 8786.
E-mail address: igaki-tky@umin.ac.jp (H. Igaki).

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1. Background

Intensity-modulated radiotherapy (IMRT) is a technique that spares OARs while maintaining a high dose to the planning target volume. In order to avoid radiation dose to certain areas of the body in IMRT planning, these areas have to be contoured and defined as OARs on the treatment planning system. OARs are generally contoured according to the outline of the organ as demonstrated by CT or MRI. But a part of the organ with a specific function is difficult to protect, because the procedures to fuse functional images to radiotherapy planning CT images have not been fully formulated.

Recent advances in imaging technologies have enabled us to determine the brain areas of specific functions which are not visible in conventional CT or the conventional sequence of MRI. One of the newer imaging technologies includes diffusion tensor tractography. These images can depict the lineage of neuron fibers from the diffusion anisotropy of water in the neuronal axon. Using this method, the putative position of specific neuron fibers in the white matter, such as the corticospinal tract, optic radiation, arcuate fasciculus, can be known.[1–4] For patients with brain tumors who are undergoing neurosurgery, operative procedures have become safe, incorporating diffusion tensor tractography into the preoperative workup, since neurosurgeons are able to know the proximity of the tumor to the eloquent tract before surgery.[5,6] At our hospital, diffusion tensor tractography has also been fused to Gamma Knife treatment-planning MRIs, mainly for patients with arteriovenous malformation, with good clinical results.[3,4,7,8]

Treatment results of malignant glioma are not satisfactory, and various attempts to improve radiation delivery have been made to prolong the patients' survival. IMRT is one of the principal technologies applied for better dose distribution,[9] because the brain has many OARs visible on planning CT or on conventional MRI, such as the brainstem, optic pathways, eyeballs, and hippocampus. However, invisible parts, like specific neuron fibers, should be considered as OARs to reduce the morbidity rate, especially when a higher dose delivery is intended.

2. Aim

In this study, we tried to define the corticospinal tract as an OAR by fusing diffusion tensor tractography into the planning CT to diminish the dose to the corticospinal tract and use the result to conduct IMRT planning of patients with malignant glioma.

3. Materials and methods

3.1. *Patients and imaging studies*

High-grade glioma patients with pathological diagnosis confirmed by stereotactic biopsy who had been treated by 60 Gy of 3-dimensional conformal radiotherapy with concurrent and adjuvant temozolomide were selected. Their diagnostic images and treatment-planning images, respectively, were used for IMRT planning.

Diffusion tensor tractography was constructed as shown previously.[1,7] In brief, diffusion-weighted images were acquired at 1.5 T using a head coil with echo planar capability, by a single-shot spin echo-echo planar sequence (TR 6000 ms, TE 78 ms) before stereotactic biopsy. Diffusion tensors were then calculated and 3-dimensional fiber-tract maps were created using the free software dTV. The software was developed by the Image Computing and Analysis Laboratory at the Department of Radiology of the University of Tokyo Hospital, Japan, and is available online at http://www.ut-radiology.umin.jp/people/masutani/dTV.htm. A region of interest was manually drawn as seeds on an uninvolved region of the corticospinal tract that could be detected in the cerebral peduncle on the anatomical MR image (gadolinium-enhanced T1-weighted images or T2-weighted images), and another region of interest on the ipsilateral precentral gyrus as a target. Diffusion tensor tractography was reconstructed in 3-dimensional space from the seeds along the major eigenvector to trace axonal projections, and only the tracts reaching the target were displayed. Tracking was terminated when it reached a pixel with a fractional anisotropy lower than 0.18. Three-dimensional fiber-tract maps were made by marking the voxels running through the tract. The anatomical images and fiber-tract maps were blended, and the blended images were re-sliced and converted to the DICOM format by image processing software Dr. View (AJS Co. Ltd., Tokyo, Japan).

3.2. *Image fusion and treatment planning*

Treatment planning CT images were obtained with the head fixed by a thermo-plastic shell. Blended tractography images were fused to treatment planning CT images on a treatment planning system. The corticospinal tract that was displayed on the blended images was contoured manually on the treatment planning system and defined as an OAR. Gadolinium-enhanced T1-weighted images, T2-weighted images, or fluid-attenuated inversion recovery images were also fused to the planning CT in order to contour other OARs, gross tumor volumes, and clinical target volumes (CTVs). The eyeballs, lenses, optic pathways, and brainstem were contoured as OARs. CTV1 was defined as a perifocal edema with a 15-mm margin, and CTV2 was the tumor enhanced with gadolinium on MRI. PTV1 and PTV2 were defined as the corresponding CTVs plus 5-mm margins, and IMRT plans were made by the Pinnacle^3 treatment-planning system (Philips/ADAC, Milpitas, CA) to deliver 50 Gy to PTV1 and 65 Gy to PTV2 by the simultaneous integrated boost method in 25 fractions. Dose constraints are shown in Table 1. For comparison to the conventional IMRT plan, another IMRT plan was made under the same sets of dose constraints but without that for the corticospinal tract.

4. Results

Blended tractography images containing anatomical information and fiber-tract maps were constructed (Fig. 1). The

Table 1 – Dose constraints for IMRT plans.

Regions of interest	Dose constraints
PTV1	$D_{95\%} > 50$ Gy
PTV2	$D_{95\%} > 65$ Gy
Brainstem	$V_{54\,Gy} < 10\%$
Corticospinal tract	Max 50 Gy
Optic tract	Max 50 Gy
Eyes	Max 30 Gy

blended images were transferred to the treatment-planning system and fused to the planning CT images in accordance with the anatomical information contained in the blended images. The corticospinal tract fibers were contoured in the blended images, because they are depicted on the blended images of Fig. 1C. As a consequence, the corticospinal tract could be registered as an OAR on the treatment planning system, like other OARs such as eyeballs, chiasm, and brainstem.

IMRT planning was performed according to the planning objectives shown in Table 1. The plan was compared with another IMRT plan made with similar combinations of the planning objectives in Table 1, but without the dose constraint for the corticospinal tract (Fig. 2). Dose–volume histogram (DVH) analyses revealed marked dose reduction in the corticospinal tract by integrating tractography into IMRT planning (Table 2 and Fig. 3).

5. Discussion

On IMRT planning, various kinds of imaging modalities have been used for image fusion for precise definition of gross tumor volumes, clinical target volumes, or OARs. Many new imaging techniques of MRI have been invented, not only for better tissue resolution but also for visualization of components with specific functions within organs that have been "invisible" in CT or conventional-sequence MRI. One of these techniques includes diffusion tensor images. In this paper, we proposed a new IMRT planning technique that can decrease the dose to the corticospinal tract by fusing diffusion tensor tractography into the treatment planning CTs of patients with malignant glioma.

The white matter of the brain is more vulnerable to radiation than the gray matter when the changes are evaluated clinically, pathologically, or radiologically.[10–20] Steen et al. studied the effect of therapeutic radiation on the central nervous system in pediatric brain tumor patients.[10,11] Their quantitative MRI analyses revealed that a radiation dose greater than 30 Gy was associated with a spin-lattice relaxation time decrease in the white matter in a dose- and time-dependent manner 3 months after radiotherapy onwards, while such change was not detectable within the dose level under 60 Gy in the gray matter. In the spinal cord, experimental radiation injuries were also more sever in the white matter than in the gray matter.[14–17] Though a

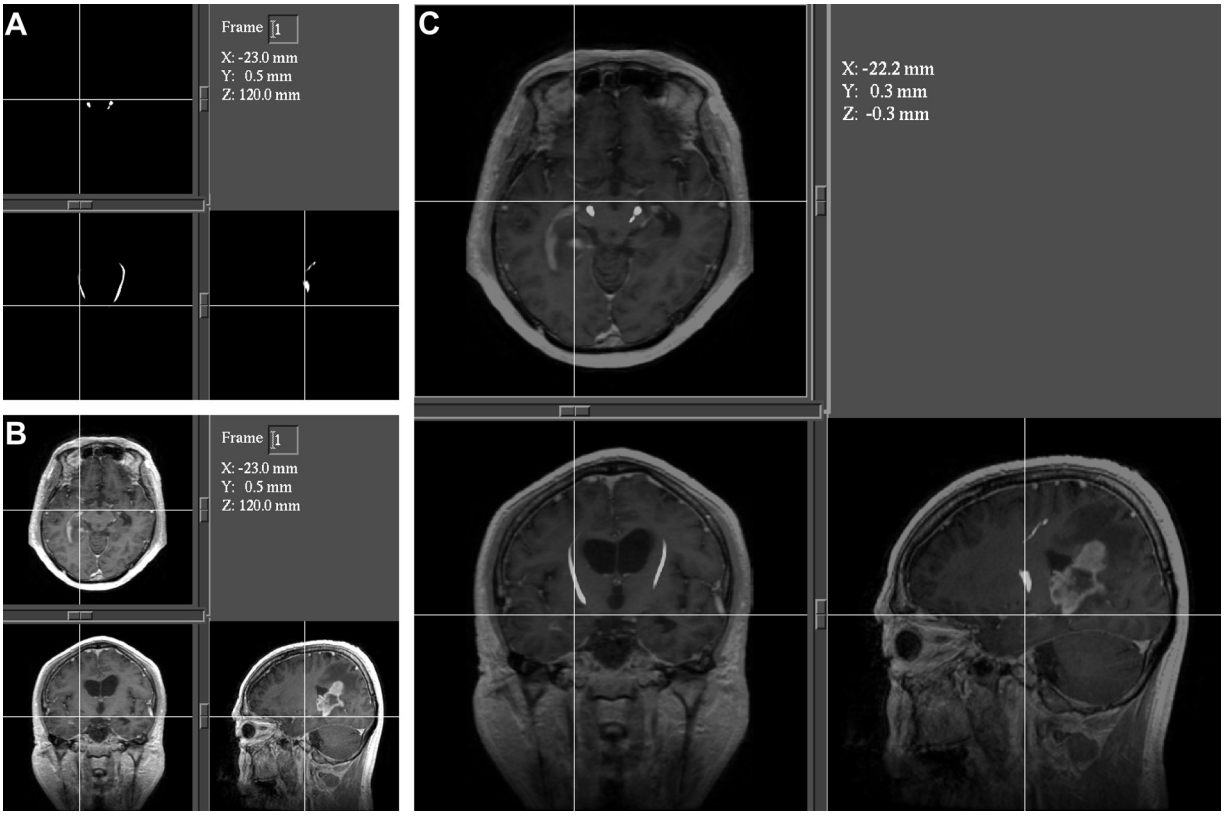

Fig. 1 – Blended image processing. Corticospinal tract passages were extracted from the diffusion tensor image (A). Gadolinium-enhanced T1 weighted images were obtained under the common spatial coordinate axis (B) and the corticospinal tract images were merged into new images containing anatomic information of the brain with clearly visible passages of the corticospinal tract (C) by image processing software Dr. View.

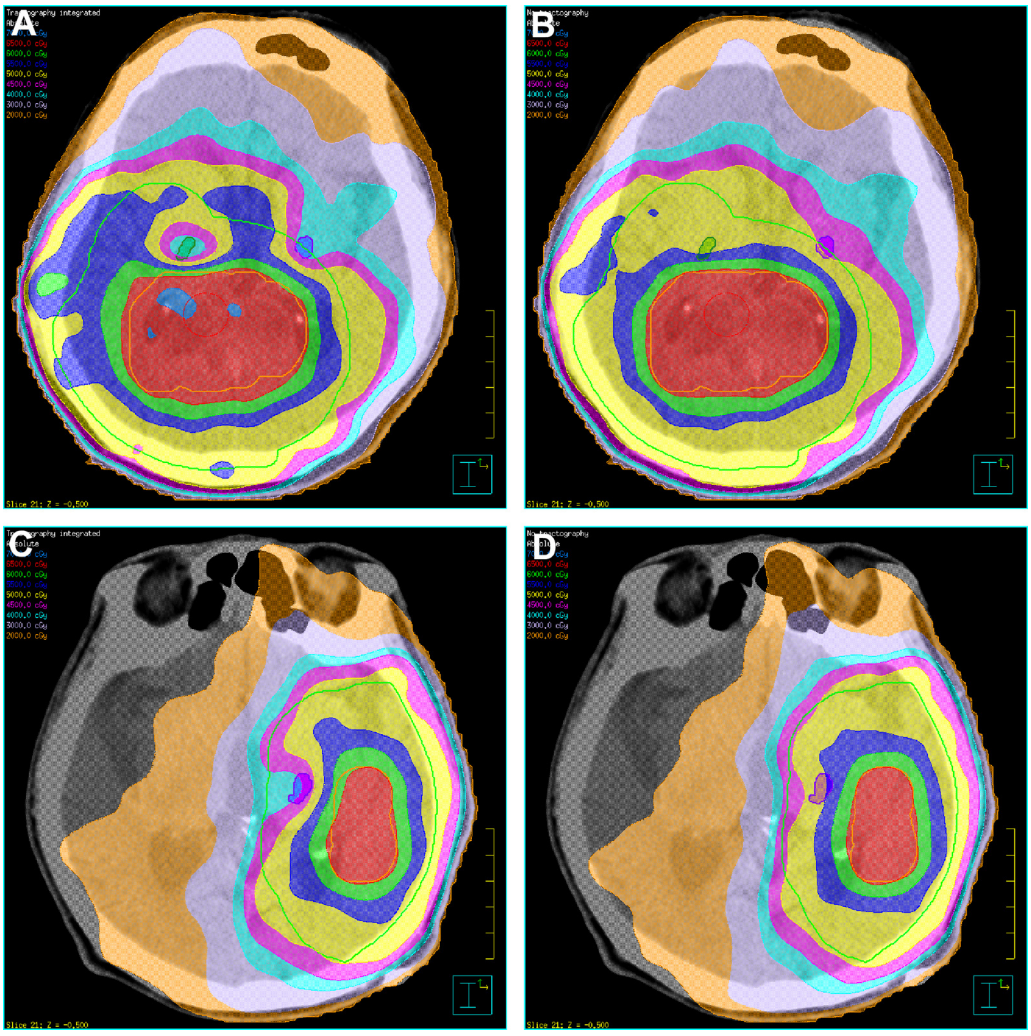

Fig. 2 – IMRT plans that protect the corticospinal tract. (A) An IMRT plan of case 1. Doses to bilateral corticospinal tracts were constrained under 50 Gy. (B) Another IMRT plan of case 1, made under the same sets of dose constraints but without that for the corticospinal tract using the same CT images as in A. (C) An IMRT plan of case 2 with the dose constraints for the corticospinal tracts. (B) Another IMRT plan of case 2 without the dose constraints for corticospinal tract using the same CT images as in C. PTV1 and PTV2 are portrayed in light green and orange, respectively; corticospinal tracts are portrayed in green (right) and purple (left).

therapeutic radiation dose of less than 50 Gy seldom induces clinically apparent impairment of neurocognitive or motor function, vascular and glial injuries can occur by a lower dose of radiation in the white matter.[18–20] The rationale of our strategy of protecting axonal fibers by tractography-integrated IMRT is based on these findings.

It has been well recognized that gross tumor volumes or clinical target volumes should be defined not only by anatomical structures that can be contoured by CT or conventional sequences of MRI but also by structures that are delineated by the functional imaging of positron emission tomography.[21–26] Chang et al. have reported IMRT that spares the primary motor cortex by the fusing of functional MRI to the planning CT.[27–29] However, similar strategies of protecting OARs by fusing functional images have not well been established.

We have used diffusion tensor tractography in Gamma Knife treatment planning of patients with arteriovenous malformation to decrease the dose to critical structures, such as the corticospinal tract, optic radiation, or arcuate fasciculus since 2004.[3,4,7] In our Gamma Knife experience, the rate of delayed motor complications was high among the arteriovenous malformation patients whose corticospinal tract dose was proved to be high by retrospective integration of diffusion tensor tractography into the dose distributions of Gamma Knife treatment plans.[30] In addition, neurological morbidities after treatment were decreased by avoiding high-dose delivery to the visualized fiber tract through the prospective integration of diffusion tensor tractography into the Gamma Knife treatment planning.[8] Our observations have three significant implications. The first is that functional structures such as neuron fibers that were “invisible” previously in the CT or conventional MRI should be protected in order to reduce post-treatment complications. The second is that the localization of the neuron fibers depicted on the diffusion tensor

Table 2 – Dose–volume statistics of the plans.

Volume	Index	Case 1		Case 2[a]	
		With constraint for CST Figs. 2A and 3A (solid line)	Without constraint for CST Figs. 2B and 3A (dotted line)	With constraint for CST Figs. 2C and 3B (solid line)	Without constraint for CST Figs. 2D and 3B (dotted line)
PTV1	$D_{98\%}$ (cGy)	6951	6768	6782	6798
	D_{mean} (cGy)	6802	6711	6697	6699
	$D_{2\%}$ (cGy)	6438	6518	6460	6500
PTV2	$D_{98\%}$ (cGy)	6573	6481	6440	6427
	D_{mean} (cGy)	5564	5480	5519	5485
	$D_{2\%}$ (cGy)	4648	4915	4802	4960
CST-R	$D_{98\%}$ (cGy)	4461	5593	–	–
	D_{mean} (cGy)	3860	5039	–	–
	$V_{50\,Gy}$ (%)	0	71.99	–	–
	$V_{40\,Gy}$ (%)	28.89	96.57	–	–
	$V_{30\,Gy}$ (%)	96.87	97.74	–	–
CST-L	$D_{98\%}$ (cGy)	4678	5255	4653	5492
	D_{mean} (cGy)	3990	4743	2597	2936
	$V_{50\,Gy}$ (%)	0.02	16.41	0	20.19
	$V_{40\,Gy}$ (%)	55.95	95.1	44.18	50.74
	$V_{30\,Gy}$ (%)	96.27	97.84	53.51	53.94

PTV = planning target volume; CST = corticospinal tract; $D_{98\%}$ = dose to 98% of the volume; D_{mean} = mean dose of the volume; $D_{2\%}$ = dose to 2% of the volume; $V_{50\,Gy}$ = % volume receiving a dose over 50 Gy; $V_{40\,Gy}$ = % volume receiving a dose over 40 Gy; $V_{30\,Gy}$ = % volume receiving a dose over 30 Gy.

[a] Right corticospinal tract was not analyzed for dose–volume statistics because of its sufficient distance from the PTV.

tractography is sufficiently reliable for clinical decision making in Gamma Knife treatment. Finally, clinical application of these tractography-based fiber-sparing techniques is feasible in the Gamma Knife treatment planning system.

After experiencing tractography-based fiber-sparing Gamma Knife treatment of arteriovenous malformation, we tried to apply these methods for another disease. Appropriate extent of clinical target volume for malignant glioma is controversial and its definitions are different among hospitals.[31,32] Therefore, we expected lower rate radiation morbidities due to corticospinal tract injury without increasing the probability of local recurrences, by applying tractography-based fiber-sparing IMRT procedures to the treatment planning for malignant gliomas.

One of the main limitations of this study is that the clinical significance of tractography has not been validated. Clinical validation of diffusion tensor tractography has been attempted by electrophysiological procedures in neurosurgical series,[33–35] integrating functional MRI,[36–38] and comparisons with known anatomical connectivity or tracer studies.[39–42] Notably, Kamada et al. confirmed the reliability of diffusion tensor imaging-based tractography by showing a strong correlation between the stimulus intensity of direct fiber stimulation during operation and the distance from the

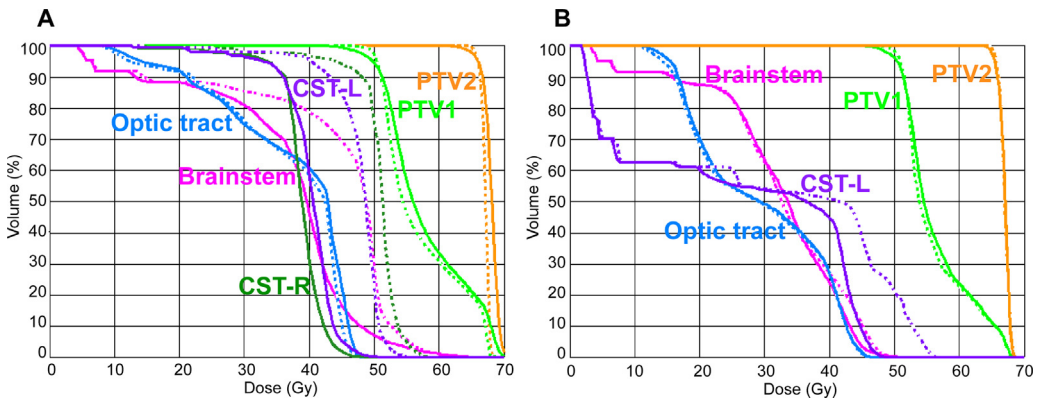

Fig. 3 – DVHs of IMRT plans. DVHs of IMRT plans of the case 1 (A) and case 2 (B) shown in Fig. 2. Solid and dotted lines represent the plans with dose constraints for the corticospinal tract (Fig. 2A and C) and those without dose constraints (Fig. 2B and D), respectively. DVH analyses revealed that the doses to the corticospinal tracts and the brainstem were diminished by integrating tractography into IMRT planning, while PTV dose coverages were comparable. Light green, orange, green, purple, pink, and light blue lines represent DVHs of PTV1, PTV2, right corticospinal tract (CST-R), left corticospinal tract (CST-L), brainstem, and optic tract, respectively.

stimulus point to the corticospinal tract on tractography-integrated neuronavigation images.[33] But the size and the extent of the fiber bundle are not necessarily reliable, because fiber-tracking is dependent on various kinds of factors such as spatial resolution and signal-to-noise ratio of the images, the reconstruction algorithm, the size and location of the region of interest drawn as seed and target, the threshold of fractional anisotropy, and the existence of crossing fibers.[10,38,43–45] There is no gold standard for the fiber-tracking technique. In this sense, we should carefully re-evaluate the clinical usefulness of this method when the tract-tracking conditions are different. Nevertheless, we believe that our experience of tractography-integrated Gamma Knife offers reliable information on the localization accuracy of the functional axonal fibers.[8,30]

Another limitation of this study is the uncertainty of therapeutic impact in terms of late radiation morbidity and local tumor control, because this is not a clinical study but only a treatment-planning study of a very limited number of patients. The patients whom this technique is applicable to are somewhat limited. The distance between the GTV and the corticospinal tract should not be too close, because the dose to the corticospinal tract that is at a very high risk of recurrences cannot be lowered. On the other hand, there is no need to avoid corticospinal tract by IMRT when it is at a sufficient distance from the GTV. However, a portion of patients, in fact, develop late neurotoxicities related to white matter changes after IMRT.[46,47] In addition, many institutions are adopting a simultaneous integrated boost IMRT technique with an accelerated fractionation schedule[48,46,49–51] for the treatment of malignant glioma, which potentially leads to an increased rate of late radiation morbidities compared with conventionally fractionated 3-dimensional conformal radiotherapy, because the alpha/beta ratio of normal brain tissue is known to be low. Dose reduction in the specific neuron fibers by tractography-integrated IMRT might allow to avoid such toxicities, even if there were limited number of patients who received benefits from corticospinal tract sparing IMRT. Viewing the feature of tract avoidance from another angle, local tumor control might be sacrificed. We selected patients whose corticospinal tract was not involved by the gross tumor (gadolinium-enhanced region) in this study; thus, the dose to the gross tumor volume was not diminished due to corticospinal tract sparing (Fig. 3). In this respect, we handled the corticospinal tract similarly as we would other "visible" OARs during the treatment planning. Therefore, we are now planning to test the feasibility and the efficacy of CST-sparing IMRT for glioblastoma patients in a clinical trial.

6. Conclusions

We developed corticospinal tract-sparing IMRT plans for patients with glioblastoma by integrating diffusion tensor tractography into the treatment-planning system. Application of this technique to IMRT planning may limit the dose to the corticospinal tract in patients with malignant glioma.

Conflict of interest

None declared.

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