Stereotactic diffusion tensor imaging tractography for Gamma Knife radiosurgery

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OBJECTIVE The integration of modern neuroimaging into treatment planning has increased the therapeutic potential and safety of stereotactic radiosurgery. The authors report their method of integrating stereotactic diffusion tensor imaging (DTI) tractography into conventional treatment planning for Gamma Knife radiosurgery (GKRS). The aim of this study was to demonstrate the feasibility of this technique and to address some of the technical limitations of previously reported techniques.

METHODS Twenty patients who underwent GKRS composed the study cohort. They consisted of 1 initial test case (a patient with a vestibular schwannoma), 5 patients with arteriovenous malformations, 9 patients with cerebral metastases, 1 patient with parasagittal meningioma, and 4 patients with vestibular schwannoma. DTI images were obtained at the time of standard GKRS protocol MRI (T1 and T2 weighted) for treatment, with the patient's head secured by a Leksell stereotactic frame. All studies were performed using a 1.5-T magnet with a single-channel head coil. DTI was performed with diffusion gradients in 32 directions and coregistered with the volumetric T1-weighted study. DTI postprocessing by means of commercially available software allowed tensor computation and the creation of directionally encoded color-, apparent diffusion coefficient-, and fractional anisotropy-mapped sequences. In addition, the software allowed visualized critical tracts to be exported as a structural volume and integrated into GammaPlan as an "organ at risk" during shot planning. Combined images were transferred to GammaPlan and integrated into treatment planning.

RESULTS Stereotactic DT images were successfully acquired in all patients, with generation of correct directionally encoded color images. Tract generation with the software was straightforward and reproducible, particularly for axial tracts such as the optic radiation and the arcuate fasciculus. Corticospinal tract visualization was hampered by some artifacts from the base of the stereotactic frame, but this was overcome by a combination of frame/MRI volume adjustment and DTI seeding parameters. Coregistration of the DTI series with the T1-weighted treatment volume at the time of imaging was essential for the generation of correct tensor data. All patients with the exception of the vestibular schwannoma cases had treatment pathology in the vicinity of eloquent tracts and/or the cortex. No new neurological deficits due to radiation were recorded at the short-term follow-up.

CONCLUSIONS Recent reports in the medical literature have suggested that white matter tracts (particularly the optic radiation and arcuate fasciculus) are more vulnerable to radiation during stereotactic radiosurgery than previously thought. Integration of stereotactic tractography into GKRS represents a promising tool for preventing GKRS complications by reduction in radiation doses to functional organs at risk, including critical cortical areas and subcortical white matter tracts.

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KEY WORDS Gamma Knife; stereotactic radiosurgery; diffusion tensor imaging; tractography; treatment planning; arteriovenous malformations

GAMMA Knife radiosurgery (GKRS), since its inception by Leksell, has been dependent on high-quality imaging for its success. Developments in neuroimaging have paralleled the evolution in techniques and indications for stereotactic radiosurgery.

The integration of modern neuroimaging into treatment

planning has increased the therapeutic potential and safety of stereotactic radiosurgery. Nevertheless, radiation-induced neuropathy remains a serious concern, particularly with arteriovenous malformations (AVMs) in eloquent locations.^{1,8}

Previous reports have focused on using separately ac-

ABBREVIATIONS ADC = apparent diffusion coefficient; AVM = arteriovenous malformation; CST = corticospinal tract; DEC = directionally encoded color; DTI = diffusion tensor imaging; FA = fractional anisotropy; GKRS = Gamma Knife radiosurgery; MPR = multiplanar reformatting; OR = optic radiation; R/VOI = region/volume of interest.

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TABLE 1. Clinical characteristics of 20 patients who underwent stereotactic DTI tractography for GKRS

Case No.	Age (yrs)	Pathology	Location	Clinical Presentation
1	47	Vestibular schwannoma	Rt CPA	Hearing loss
2	72	Metastasis (n = 1) from SCLC	Rt precentral	Incidental on surveillance MRI
3	47	AVM	Lt occipital	Tinnitus
4	50	AVM	Rt temporal	Hemorrhage, lt superior quadrantanopia
5	58	Vestibular schwannoma	CPA	Tinnitus
6	82	Vestibular schwannoma	CPA	Tinnitus
7	55	Metastases (n = 4) from renal cell carcinoma	Lt parietal	Incidental on surveillance MRI
8	72	Vestibular schwannoma	Rt CPA	Hearing loss
9	24	AVM	Occipital	Headache
10	29	Metastasis (n = 1) from melanoma	Basal ganglia	Incidental on surveillance MRI
11	32	AVM	Rt occipital	Tinnitus
12	74	Vestibular schwannoma	CPA	Deafness & ataxia
13	65	Metastasis (solitary)	Intraventricular	Incidental on surveillance MRI
14	67	Meningioma (Grade I)	Parasagittal	Seizure & lt sensorimotor deficit
15	43	Metastases (n = 7) from melanoma	Lt parietal & multiple other locations	Rt sensorimotor deficit
16	48	Metastases (n = 2) from melanoma	Lt frontal & cerebellar	Mild rt sensorimotor deficit
17	59	Metastases (n = 7) from SCLC	Brainstem & multiple other locations	Incidental on surveillance MRI
18	38	AVM	Lt frontotemporal	Tinnitus
19	59	Metastases (n = 2) from melanoma	Lt posterior frontal & rt frontal	Incidental on surveillance MRI
20	56	Metastases (n = 2) from NSCLC	Rt occipital & lt thalamic	Hemianopia & mild rt upper-limb weakness

CPA = cerebellopontine angle; NSCLC = non-small cell lung cancer; SCLC = small-cell lung cancer.

quired tractography images and fusing them with stereotactic treatment images in order to analyze dosimetry to critical fiber tracts and improve treatment planning.^{11,12,13} This process has also been recently reported using other radiosurgical platforms.^{5,16} The use of diffusion tensor imaging (DTI) has been reported to reduce the risk of motor complications after radiosurgery.⁹

We present our method of integrating stereotactic DTI tractography into conventional treatment planning for GKRS.

Methods

Twenty patients who underwent GKRS made up the study cohort. They consisted of 1 initial test case (a patient with a vestibular schwannoma), 5 patients with AVMs, 9 patients with cerebral metastases, 1 patient with parasagittal meningioma, and 4 patients with vestibular schwannoma. The clinical characteristics of the patients are listed in Table 1.

Stereotactic 3D Imaging

On the day of GKRS, the patient was immobilized in a Leksell model G, MRI-compatible stereotactic frame for stereotactic 3D anatomical MRI. All studies were performed using a 1.5-T magnet (Achieva; Philips) with a single-channel transmit/receive head coil. Our standard GKRS treatment protocol, consisting of T1- and T2-weighted sequences (with contrast), was performed. The T1-weighted 3D fast field echo MRI study consisted of 100 sequential, 1.5-mm-thick axial slices with a resolution of 256 × 256 pixels over an FOV of 210 mm with 3D T2-

weighted 512 × 512-matrix 1.5-mm-thick axial slices as required. In the cases of AVMs, cerebral stereotactic angiography was also performed. The T1- and T2-weighted treatment sequences were transferred to GammaPlan via a picture-archiving and communication system for treatment planning.

Stereotactic DTI

High-directional DTI was performed at the time of standard GKRS protocol MRI (T1 and T2 weighted) for treatment, with the patient's head secured by a Leksell stereotactic frame and our standard "birdcage" transmit/receive head coil.

We used a high-directional resolution DTI sequence single-shot spin echo–echo planar sequence (TR 2700 msec, TE 160 msec), acquiring 60–68 interleaved, contiguous 2-mm-thick axial images with no cardiac triggering.

A data matrix of 512 × 345 pixels over an FOV of 210 × 210 mm was obtained. Diffusion gradients were applied in 32 noncollinear independent axes by using a b value of 0 and 1000 sec/mm². Each complete DTI data set required an additional 14–16 minutes of MR scanning time. The DTI and the T1- and T2-weighted data sets were transferred via CD to a StealthViz (Medtronic, Inc.) workstation for postprocessing.

DTI Tractography

DTI postprocessing was performed by means of commercially available software (StealthViz). This software is an additional component of established intraoperative neuronavigational software already in clinical use for pre-

FIG. 1. Screenshot of the tractography graphic user interface; demonstration of bilateral OR tracts in a patient with a right-sided mesial temporal AVM with previous hemorrhage and established superior quadrantanopia.

operative planning and tract generation for cranial neurosurgery.⁴ It uses the deterministic Fiber Assignment by Continuous Tracking algorithm developed by Mori et al. at Johns Hopkins.¹⁴ This is a deterministic approach that uses the average axonal orientation within a voxel to estimate axonal projections, based on user-defined variables such as the fractional anisotropy (FA) and the maximum tract angle. Probabilistic algorithms, although allowing greater tract exploration into the gray matter,² take much longer to compute and thus are not as amenable to interactive exploration of fiber tracts.

Several processing steps were required to build a DTI color map. These included gradient assignment, gradient registration, coregistration with the volumetric T1- and T2-weighted treatment sequences, and tensor computation. This resulted in the creation of FA-, apparent diffusion coefficient (ADC)-, and directionally encoded color (DEC)-mapped sequences. The image fusion function permitted visualization of the T1- or T2-weighted sequences with superimposition of the DEC sequences to aid fiber tracking (Fig. 1).

Tensor preparation is perhaps the most critical step in ensuring that the software generates anatomically correct tracts. Background masking is performed to eliminate air (represented by blue) by adjusting the thresholding. The correct gradient protocol must be selected according to the MR equipment manufacturer's protocol, e.g., Philips 32 gradient overplus off. The correct b value (1000) must also be selected per the protocol used. The gradient list must

be checked to ensure correct alignment, and this is color coded. Incorrect gradient alignment will result in incorrect vector directions and erroneous tensor computation.

Gradient registration needs to ensure correct identification of the B0 sequence from the imported DTI series. Automatic coregistration of the DTI series with the B0 sequence is performed and verified. Coregistration involves selecting the T1-weighted treatment volume as the Reference Exam, and the B0 and T2-weighted sequences are then autoregistered and verified. Finally, tensor computation is performed, resulting in generation of the selected FA, DEC, and ADC sequences. It is important to verify correct colorization of the DEC sequence. The DEC sequence is viewed with either the T1- or T2-weighted sequence in fusion mode to aid identification of tract seeding points and to ensure the anatomical accuracy of the coregistration process.

DTI fiber tracking is performed by selecting the Fiber Tracking Tool, which permits the creation and display of tracts. Tract seeding was performed by defining a rectangular region/volume of interest (R/VOI) in the displayed coregistered data set. The definition of the R/VOI depended on the fiber structures to be displayed (i.e., optic radiation [OR], corticospinal tract [CST], and so on).

The methods for R/VOI selection of the major white fiber tracts are well described in the literature.^{3,15} The default value of angulation threshold was 45°, and the FA threshold was 0.20. Midpoints and end points can also be chosen, depending on the tract to be visualized.

FIG. 2. Screenshot of an imported CST with segmentation in GammaPlan and creation as a volume at risk.

To complete the process, the generated tracts were rendered as 3D objects by selecting multiplanar reformatting (MPR) in the Fiber Tracking Tool and by clicking the Surf Box in the 3D Object Tool Card to view the tract. The 3D Tract Object could be edited with the Segmentation Screen.

The generated tracts were exported with the navigation examination (T1-weighted) and a hybrid examination (T1-weighted with superimposed/burned 3D tract) in DICOM format using the 3D Object Data dialog. Tract studies were burned to DICOM CD for transfer to GammaPlan.

Integration Into GammaPlan

With GammaPlan open and with the standard treatment T1- and T2-weighted images already imported and verified, the CD containing the tract data was uploaded to the treatment workstation. The tractography data set was imported into GammaPlan (version 10.1; Elekta Instruments AB) using the native DICOM CD import function. The DICOM data sets were imported into the treatment planning session and coregistered with the main T1-weighted stereotactic treatment volume.

The imported tract images appeared in gray scale in the DICOM format and were color coded with GammaPlan to facilitate clear identification. The GammaPlan software allowed critical tracts to be segmented as a structural volume and integrated into GammaPlan as an “organ at risk” during shot planning (Fig. 2). Furthermore, tract volumes could be subjected to standard dosimetric analysis using

the measure function. A summary of the steps required to fully integrate DTI data into GammaPlan is given in Fig. 3.

Results

Stereotactic DTI tractography was successful in generating the appropriate ADC, FA, and DEC sequences in all except for the first test case (19 of 20 cases). It was recognized that the first test case error was due to a rotational mismatch between the orientation of the DTI volume and the stereotactic T1-weighted treatment volume at the time of image acquisition. This error was overcome by creating an MRI protocol, which matched the spatial orientation of the DTI volume with the 3D stereotactic T1-weighted volume at scanning.

All successful cases were reviewed on the tractography workstation at the time of GKRS treatment planning to assess any pertinent anatomy or structures at risk. The cases of vestibular schwannoma were used as controls for the major tracts and to develop proficiency with tract generation because it is recognized that the technique is operator dependent. Although tractography has previously been used to identify the facial nerve, it was not performed in this study.

In the case of cerebral metastases, we observed that tractography provided additional useful clinical information for treatment planning (Fig. 4), which accounted for a recent deterioration in the patient’s clinical symptoms

FIG. 3. Diagram summarizing the steps required to integrate stereotactic DTI into GammaPlan.

(hemianopia and hemiparesis). Tractography clearly demonstrated compression of the OR by the metastatic deposit and associated edema. Displacement and compression of the CST by a metastatic deposit and associated edema were also evident.

A selected solitary melanoma metastasis in proximity to the thalamus (25 Gy at 45% isodose) was selected

for dosimetry with $\leq 1\%$ of the CST volume receiving > 12 Gy with a maximum dose of 25 Gy.¹⁰ The patient did not develop any neurological deficits and was treated for a new contralateral hemispheric deposit 7 months later with demonstrated good radiological response to her previous treatment.

All 5 cases of AVMs had their selected generated tracts

FIG. 4. OR compression and CST displacement demonstrated by DTI. The patient presented with progressive hemianopia right-sided pronator drift with mild right-sided hemiparesis. The patient had metastatic lung cancer, with previous whole-brain radiation therapy for left thalamic deposit (resistant) (**A and B**). The patient underwent salvage GKRS with new right occipital deposit (**C**). The deposits received 19–20 Gy to the 42%–48% isodose, achieving 98%–99% coverage of the lesions (**D**).

retrospectively imported into GammaPlan for dosimetric analysis of the tracts at risk. These data are summarized in Table 2. Our reported data are within the previously published tract tolerances summarized in Table 3.

One patient had staged (by feeding vessel) treatment of a large-volume AVM adjacent to the CST (Fig. 5). Follow-up at the second-stage treatment 6 months later demonstrated early nidus volume reduction and no neurological deficit.

Three of the AVMs are postgeniculate and pose risk of causing damage to the OR.³ During this very short follow-up period (6–12 months), none of the patients developed a new deficit as a result of their GKRS.

Discussion

Recent reports in the medical literature have suggested that white matter tracts (particularly the OR¹² and arcuate

fasciculus¹³) are more vulnerable to radiation during SRS than previously thought. Traditional estimates for the risk of radiation necrosis⁷ may not be predictive enough, especially when the pathology is adjacent to major fiber tracts. Integration of stereotactic tractography into GKRS represents a promising tool for preventing GKRS complications by reduction in radiation doses to functional organs at risk, including critical cortical areas and subcortical white matter tracts. This has been demonstrated by Koga et al.,⁹ who reported that the integration of CST DTI into GKRS planning for AVM reduces the incidence of motor complications without compromising obliteration rates.

The use of DTI is not exclusive to GKRS, and other centers have reported integrating both DTI and functional MRI into linear accelerator systems to aid treatment planning.^{5,16} They have also reported problems with coregistration accuracy.⁵

TABLE 2. Treatment data of DTI with dosimetry for 5 patients with AVMs

Case No.	Location	Prescription Dose & Vol	Tract at Risk	Tract Dosimetry	Clinical Outcome
3	Lt occipital	20 Gy @ 43%, 95% of 7.21-cm ³ AVM	OR	Max dose 6.45 Gy	No clinical change
4*	Rt temporal	25 Gy @ 51%, 96% of 3.54-cm ³ AVM	OR	Max dose 16.6 Gy to Meyers loop; 4 Gy to optic nerve & chiasm	No clinical change
9	Rt occipital	25 Gy @ 43%, 95% of 4.30-cm ³ AVM	OR	Max dose 11.40 Gy	No clinical change
11	Rt occipital	20 Gy @ 44%, 95% of 5.19-cm ³ AVM	OR	Max dose 5.5 Gy	No clinical change
18	Rt frontotemporal	22 Gy @ 42%, 95% of 14.36-cm ³ AVM	CST	Max dose 8.1 Gy	No clinical change

* Case 4 presented with hemorrhage and left superior quadrantanopia.

TABLE 3. Review of DTI and tract tolerance in the GKRS literature

Authors & Year	Tract Studied	Tract Tolerance
Maruyama et al., 2009	Arcuate fasciculus	Frontal, 10 Gy; temporal, 6 Gy
Maruyama et al., 2007	OR	<8 Gy
Maruyama et al., 2005	CST	Tract vol <25 Gy, maximum dose 28 Gy
Maruyama et al., 2008	Pyramidal tract	Pyramidal tract <23 Gy ideally outside 20-Gy isodose; internal capsule more sensitive

Our reported technique of stereotactic DTI goes some way toward improvement upon the limitations of previously reported techniques. The inherent problem of spatial accuracy and distortion induced by the coregistration process when DT images are acquired nonstereotactically is improved upon by acquiring the images stereotactically at the time of treatment imaging. Ensuring that the spatial orientation of the DTI volume is matched with the 3D stereotactic T1-weighted volume at MRI is a critical step for correct gradient alignment.

Correct gradient alignment is required for correct vector direction and is the key to tensor computation. It also ensures proper coregistration with the T1-weighted treat-

ment series. The postprocessing takes approximately an additional 15 minutes plus another 10 minutes to integrate the tract data into GammaPlan (depending on the complexity of the tract shape). Another potential use of integrated DTI is that the Dynamic Shaping function of GammaPlan may be used to move treatment beams away from critical tracts when dosimetry demonstrates that the tolerance dose may be exceeded.

Conclusions

The utility of DTI in GKRS will no doubt benefit from advances in stereotactic frame design, which will allow the use of conventional multichannel coils and imaging at higher field strength with less image distortion. Further development is required to improve the integration of DTI into the treatment planning software and to increase the ease of operator use. DTI has limitations and is user dependent; it is likely to be superseded in the future by even higher-resolution techniques in tractography involving probabilistic techniques.⁶

The aim of our study was to demonstrate the feasibility of our technique and to address some of the technical limitations of previously reported techniques. Further studies using DTI are required to increase our knowledge of specific tract and critical cerebral structure radiation tolerances to better improve the therapeutic potential and safety of GKRS.

FIG. 5. Integration of DTI into treatment planning for AVM: 20 Gy at 42% isodose adjacent to the CST (maximum dose 8.1 Gy).

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Disclosures

Mr. Sabin is a consultant for HCA International.

Author Contributions

Conception and design: Gavin. Acquisition of data: Gavin. Analysis and interpretation of data: Gavin. Drafting the article: Gavin. Critically revising the article: both authors. Reviewed submitted version of manuscript: Gavin. Approved the final version of the manuscript on behalf of both authors: Gavin. Study supervision: Sabin.

Supplemental Information

Previous Presentations

Portions of this work were presented as a plenary oral presentation (abstract no. 147) at the 18th International Leksell Gamma Knife Society meeting in Amsterdam, the Netherlands, May 15–19, 2016.

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