Original Research Article

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Progressive alterations of perilesional brain tissue after Gamma Knife stereotactic radiosurgery: a diffusion tensor imaging study

Abstract

Introduction: To search for microstructural lesions of normal-appearing cerebral white matter surrounding a tumor or a vascular lesion, after single-fraction stereotactic Gamma Knife (GK) radiosurgery.
Methods: In 43 patients with different brain lesions, magnetic resonance including diffusion tensor imaging (DTI) was performed before and after GK radiosurgery and change of parameters was measured in areas surrounding the lesion.
Results: Outside the lesion, there was an increase in mean diffusivity (MD) and radial diffusivity (RD) between 2.1% and 3.4% in the 15–10 Gy and in the 10–5 Gy perilesional isodose volumes, which reached statistical significance (paired *t*-test) for the MD and RD values in both volumes ($P \leq 0.05$) and correlated to the delay from treatment ($P<0.01$ resp. $P<0.05$). The only significant change in the fractional anisotropy values was a decrease in the 10–5 Gy isodose volume ($P \leq 0.01$), which correlated to the radiation dose applied ($P<0.05$).
Conclusion: We report some minor, but nevertheless significant changes in DTI parameters in normal-appearing perilesional brain tissue after GK radiosurgery progressing with time, which partially may be induced by the radiation itself and partially may be due to indirect effects of lesion reactions to the radiation. Follow-up studies are necessary for further characterization of these changes and assessment of their time course.

Keywords: Diffusion tensor imaging (DTI); Gamma Knife radiosurgery; perilesional alterations.

DOI 10.1515/ins-2014-0009
Received September 1, 2014. Accepted February 2, 2015.

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Introduction

The great advantage of stereotactic radiosurgery in delivering very high doses with high conformity to a specific target has resulted in an enormous increase of applications, especially in lesions of the central nervous system (CNS). It is generally assumed that due to a steep decline in the radiation gradient, the surrounding perilesional tissue can be spared from radiation damage. However, some serious late events like radionecrosis are well-known complications: up to 6% after Gamma Knife (GK) treatment of arterio-venous malformations (AVMs) [6] and up to 14% after linear accelerator stereotactic radiosurgery of brain metastases [3]. Here, the adverse event usually results from the treatment of a large volume, mainly the lesion itself, and the resulting vascular damage [1]. But if the volume is small enough (below 0.1 mm^3), single-fraction doses up to 45 Gy may

be tolerated by the brainstem in stereotactic radiosurgery of the trigeminal nerve without clinical consequences [29].

However, the radiation tolerance of normal CNS tissue has certain limits. While in conventional fractionation, doses below 60 Gy are usually tolerated well in the clinical setting [8], single-dose radiation of the rat brain with 30 Gy in an area of 4.7 mm in diameter had a 10% risk of magnetic resonance (MR) changes during the next 2 years [12]. The radiation tolerance of the spinal cord appears to be at a similar range with a 50% probability of clinical deficit in case of a 20-Gy stereotactic radiation applied to one half of the cord in a swine model [18]. Small structures like cranial nerves are more susceptible: single doses to the optic nerve above 10–12 Gy can induce clinical deficit [17], which is well within the range of the perilesional dose in most types of radiosurgeries. If histology is applied, acute cell death and sustained changes in neurogenesis and in microglia have even been observed in the rat hippocampus after GK treatment with single doses above 3 Gy [21].

The present study was performed to find subtle changes in the perilesional tissue after stereotactic radiation which might not be evident in routine MR scanning or clinical follow-up but could be shown by measuring the parameters of diffusion tensor imaging (DTI). The method is highly sensitive in detecting structural alterations mainly in the white matter and has been applied successfully to all types of cerebral degeneration. Because of this, DTI has been suggested to be a useful tool for noninvasive monitoring of radiation-induced brain injury [24]. From animal studies in rats using stereotactic radiation [25] and follow-ups in humans after conventional radiotherapy [28], it is known that changes in DTI parameters depend on the time delay after treatment, and certainly on other factors like the type, size, and vascularization of the lesion itself [15] and even the patients' age [27] could influence the degree of alterations in the perilesional tissue.

Materials and methods

This prospective study has been approved by the local Ethic Committee and was started in early 2011 and ended in the first half of 2014.

Patients

Included were all patients regardless of the kind of lesion treated at our GK center (i) with MR scans (including DTI) performed within 2 months before single-dose stereotactic radiosurgery and (ii) without obvious tissue alterations such as tumor enlargement, development of edema, or obvious tumor shrinkage on T1- and T2-weighted images on MRI follow-up (including DTI) obtained at least 5 months after treatment. Because of these strict criteria, only slightly more than half of the 77 patients, in whom DTI imaging before and after GK treatment was available, entered into the study. We included 43 patients showing stable conditions in routine MR sequences before and 9.6 (5–20) months after GK treatment mainly suffering from meningiomas or AVMs (Table 1).

Gamma Knife treatment

Stereotactic radiosurgery was performed on a Leksell GK unit (Model 4, Elekta/Stockholm, Sweden). Depending on the size and localization, the margin dose applied to AVMs varied from 18 to 25 Gy; to meningiomas varied from 12 to 18 Gy; to schwannomas varied from 12 to 13 Gy, etc. (Table 1). Some 5 AVMs were central and 7 AVMs were peripheral ones, and both received margin doses between 18 and 25 Gy. From the 16 meningiomas, 5 were localized infratentorial and 4 supratentorial near the skull base, and 7 meningiomas were situated over the convexity. All infratentorial and basal meningiomas were treated with a margin dose of 12–15 Gy and others with 14–18 Gy. All 5 schwannomas were related to the 8th cranial nerve and received 12–13 Gy. Depending on their hormonal status, 2 of the adenomas were treated with 13 and 16 Gy and the other 2 with 25 and 30 Gy. One infratentorial cavernoma was radiated with 14 Gy and 3 supratentorial cavernomas with 16–20 Gy. The treatment was planned on a Leksell GammaPlan workstation (Version 10.1, Elekta/Stockholm, Sweden) by adjusting the 50% isodose line to fit the outer border of the lesion and to avoid undue radiation to sensible structures like the optic system or the cochlea, keeping the coverage index as high as possible (mean: 97.0%).

Table 1: Lesion types, radiation dose, and follow-up time (average and range).

Pathology	Number of cases	Volume of lesion (mL)	Margin dose (Gy)	Follow-up time since treatment (months)
Meningioma	16	8.8 (0.7–22.5)	14.2 (12–18)	10.6 (6–20)
AVM	12	9.98 (2.4–30.3)	21.0 (18–25)	9.4 (6–19)
Schwannoma	5	4.86 (2.0–7.8)	12.6 (12–13)	10.0 (5–15)
Adenoma	4	3.96 (1.9–6.4)	21.0 (13–30)	10.5 (7–19)
Cavernoma	4	1.33 (0.3–2.9)	17.5 (14–20)	7.0 (6–8)
Others[a]	2	6.90 (3.1–10.7)	12.0	6.5 (5–8)

[a]One gliomatous cyst and one chordoma.

Magnetic resonance imaging

Magnetic resonance imaging was performed on a 3-Tesla scanner (Achieva, Philips/Best, Netherlands). Apart from the routine T2-, FLAIR-, and T1-weighted sequences before and after injection of contrast medium, the following DTI sequence was measured: 32 gradient directions, b=0 and 800 mm²/s, measured voxel size 2×2×2 mm³, 60 slices covering the whole head, SENSE factor 2, scanning time 4.5 min.

Postprocessing

From the available DTI data, maps of mean fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) were calculated by using the software package MRI-studio (www.mristudio.org). Thereafter, maps were coregistrated to the T2-weighted images of the pretreatment scan by the coregistration facility of Statistical Parametric Mapping (SPM, www.fil.ion.ucl.ac.uk/spm). Using the Leksell GammaPlan workstation (Elekta/Stockholm, Sweden), the isodose lines from the treatment plan (50% treatment isodose line as well as the 15, 10, and 5 Gy isodose lines) were then transferred to the pretreatment T2-weighted images using these images as the basis and adjusting the treatment plan by the coregistration modality of the system. Further postprocessing was done by the software ImageJ (rsbweb.nih.gov/ij) by copying the isodose lines, transferring them into the FA-, MD-, and RD maps as volumes of interest (VOIs, Figure 1), and then measuring the extensions of the areas and the parameter values. Area-adjusted mean values were calculated and finally, the differences between the first and second examination were corrected for scanner-dependent difference of parameters between the nonradiated areas. In those 21 cases with a margin dose below 15 Gy, where the 15-Gy isodose line was inside the area surrounded by the margin isodose line, the 15–10 Gy isodose VOI was not measured.

Special care was taken to exclude from the perilesional VOIs all areas not showing the usual intensity of cerebral tissue like gliosis, cerebro-spinal fluid (CSF), partial volume effects or iron deposits due to hemorrhages, so that within these VOIs, evaluation was confined to normal brain tissue. From the lesion area within the 50% isodose line, we only excluded areas definitively belonging to CSF spaces or bone, so that here, the whole lesion was included. Because this procedure appeared to be rather operator-dependent, evaluation was performed by one experienced neuroradiologist in all cases (Peter Stoeter). In addition, we determined the inter-observer agreement by calculating the intraclass correlation coefficient (ICC) in five patients additionally evaluated by a second person – a trained technician from the scanning team (Jairo Oviedo).

Using SPSS (http://www-01.ibm.com/software/de/analytics/spss/) we compared DTI parameters measured before and after GK radiosurgery within the 50% isodose VOIs, the 15–10 Gy isodose VOIs and the 10–5 Gy isodose VOIs by paired t-test for significance of difference. In addition, we applied a multivariate analysis of variance (MANOVA) to correct the mean values taken from these VOIs for delay time from treatment, lesion size, margin dose applied, and patients' age. We also calculated a post-hoc Scheffé test for differences of results between lesion types. Finally, we performed a partial correlation analysis correlating the MANOVA-corrected differences of the DTI parameter values before and after treatment to the delay time, lesion size, margin dose, and patients' age, using one of these items as a core variable and the remaining ones as control variables. The level of significance was set to 95%.

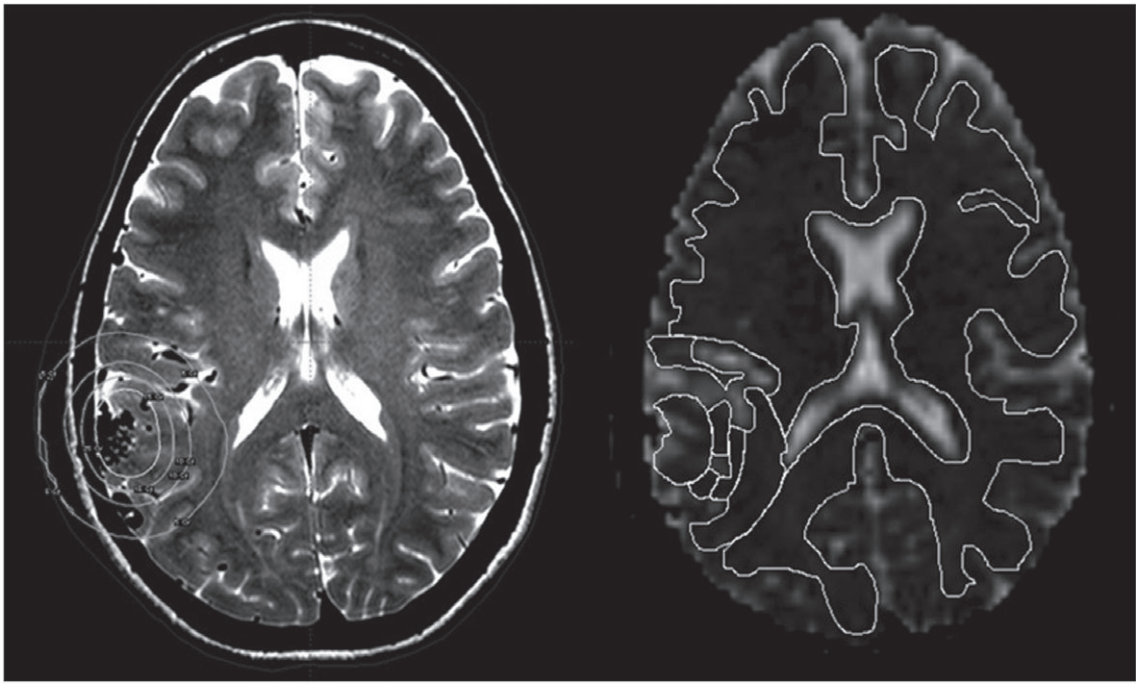

Figure 1: Gamma Knife treatment plan coregistered to T2 image of pre-treatment MR (left image) and copied isodose lines, complemented by outline of area <5 Gy isodose line, transferred as ROIs to coregistered MD map of the same examination (right image).

Results

Reproducibility of results between measurements and raters

As a measure of reproducibility between measurements, we calculated the difference in the DTI parameter values between the pre-treatment and follow-up examination in the brain areas outside the irradiated volume (<5 Gy) and got an average deviation of below 1% (FA: 0.1%±3.8%; MD: 0.7%±2.6%; RD: 0.3%±3.3%).

The calculation of the ICC between the two trained raters was high for all 3 DTI parameters (≥0.982).

Changes in DTI parameters after stereotactic radiation

After stereotactic radiosurgery, we observed a decrease in FA and an increase in MD and RD. The changes in MD and RD were more pronounced within the lesion as represented by the VOI inside the margin isodose line, but did not exceed 5.4% on average. Outside the lesion, there was an increase in the corrected values of MD of 2.5% and of RD of 3.4% in the 15–10 Gy isodose VOI as compared to an increase of 2.1% and 3.0% for both parameters in the 10–5 Gy isodose VOI. The FA values showed a slight reduction of 1.7% and 1.8% in the corresponding VOIs and of 4.8% inside the margin isodose line. The difference of the corrected parameter values before and after radiosurgery reached statistical significance (paired *t*-test) for all MD values and for the RD values in the 15–10 and 10–5 Gy isodose VOIs ($P \leq 0.05$) and for FA in the 10–5 isodose VOI ($P \leq 0.01$) (Table 2).

Correlation of changes in DTI parameters to the radiation dose, isodose volumes, patients' age, time interval after treatment, and difference in DTI parameter changes between lesion types

Within the margin dose VOI, the decrease in (corrected) FA values correlated significantly to the radiation dose applied, and the increase in MD and RD values correlated to the margin dose VOI volume and the delay from treatment ($P<0.01$ for MD and $P<0.05$ for RD). Outside the margin dose VOI, there was a significant correlation between the increase in MD and RD values and the delay from treatment in the 15–10 Gy VOI ($P<0.01$) and for the increase in MD values and the delay time in the 10–5 Gy VOI ($P<0.05$, Figure 2). Outside the lesion, there was no

Table 2: DTI parameters before and after GK radiosurgery corrected for scanner-dependent deviation between nonradiated areas (mean, standard deviation) and difference between average values in percentage before and after radiosurgery, corrected for margin dose VOI volume, margin dose applied, delay since treatment, and patients' age by MANOVA).

	FA			MD			RD		
	Pre	Post	Δ (After correction, in %)	Pre	Post	Δ (After correction, in %)	Pre	Post	Δ (After correction, in %)
Margin Dose VOI	270.4±57.5	266.2±65.3	−4.8±16.6	1280.1±316.5	1329.5±315.6[a]	+4.8±13.4[bb,cc]	1112.0±290.1	1157.9±291.7	+5.4±16.8[b,c]
15–10 Gy VOI	329.3±76.4	322.5±72.4	−1.7±8.6	848.9±72.9	870.5±89.6[a]	+2.5±5.2[cc]	713.5±119.0	743.1±183.2[a]	+3.4±7.2[cc]
10–5 Gy VOI	364.2±86.6	357.2±83.2[aa]	−1.8±4.9[d]	830.5±117.9	849.1±133.8[a]	+2.1±5.1[c]	667.9±134.9	688.4±152.9[a]	+3.0±9.3

[a]Level of statistical significance in paired *t*-test of parameter values: [a]$P<0.05$; [aa]$P<0.01$.
[b]Correlation of difference of parameter values to volume of margin dose VOIs: [b]$P<0.05$; [bb]$P<0.01$.
[c]Correlation of difference of parameter values to delay after treatment: [c]$P<0.05$; [cc]$P<0.01$.
[d]Correlation of difference of parameter values to margin dose applied: $P<0.05$.

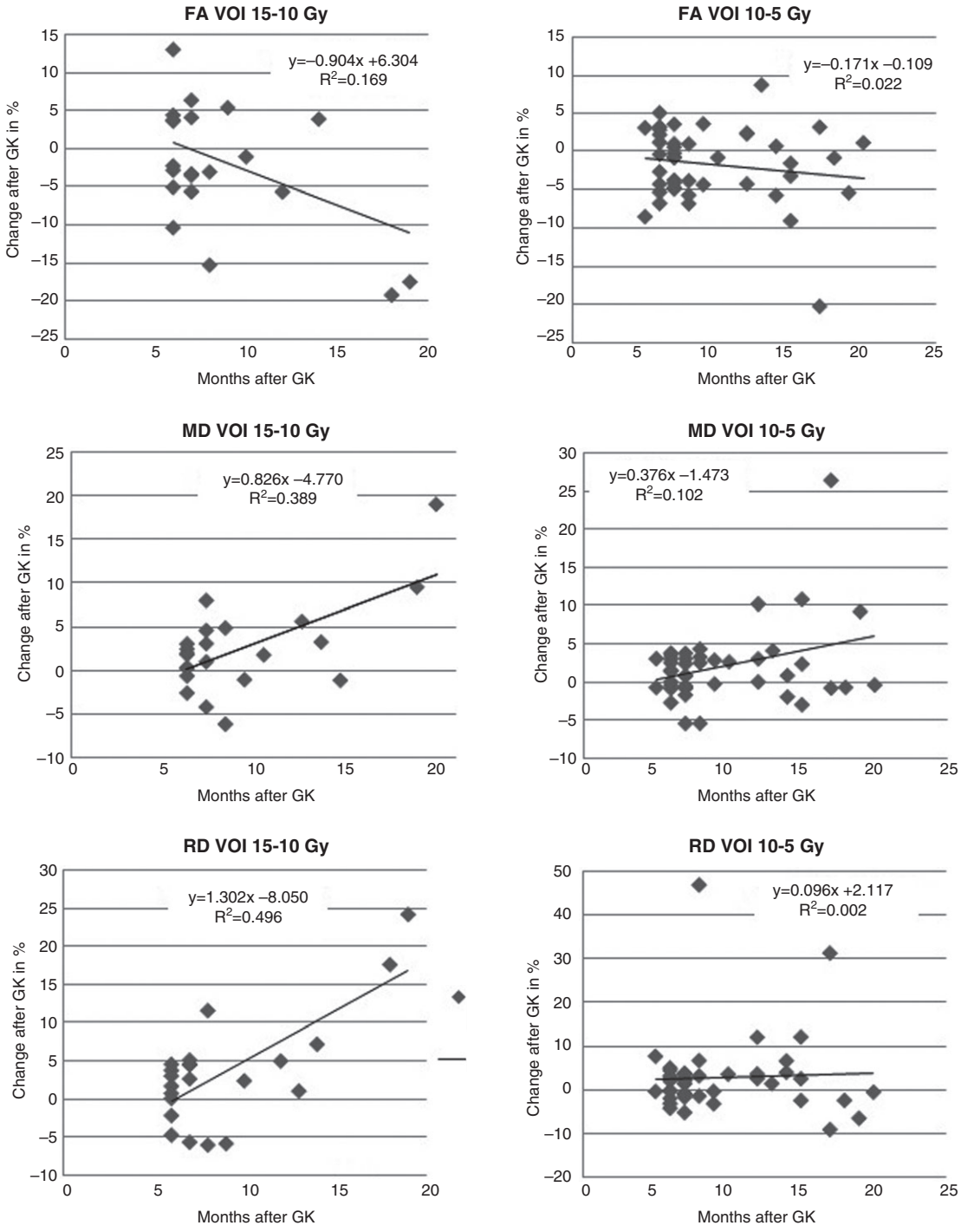

Figure 2: Changes of DTI parameters after stereotactic radiation in percentage, progressing with time after treatment.

significant correlation between any change of DTI parameters and the margin dose VOI volumes or the radiation dose applied to this VOI. The age of the patients did not correlate to any change of DTI parameters, and the post-hoc Scheffé test for significance of DTI parameter changes between lesion types did not show any significant results.

Discussion

As expected because of the steep decline in the radiation gradient outside the lesion in GK radiosurgery, we did not observe any important changes in the normal brain tissue around lesions after treatment by GK radiosurgery. However, although the changes were small with a mean of

maximal 3.4%, they were well above the changes within nonradiated tissue between two measurements, and some of these differences, mainly the MD values, reached statistical significance in the paired *t*-test. However, there were no significant correlations to the radiation dose applied. What does this mean?

Considering the lesion itself, the statistical significant correlation of only one parameter (FA) and radiation dose is not surprising because a variety of several highly different lesions was included in the study as AVMs, meningiomas, adenomas, neurinomas etc., and every variety might have reacted in a different way. According to our own results in AVMs not reported here, these changes obviously depend on the degree of occlusion, whereas tumors may develop different degrees of edema and necroses related to their histology [19]. Especially in schwannomas the response of MD values to stereotactic radiation varies with time and its course may be used as an early prediction of treatment outcome [16]. The fact that we did not see significant differences in DTI parameter changes between the various types of lesions in our post-hoc Scheffé test may be due to the rather small numbers of cases included in some of these groups.

As has been pointed out before, our focus of interest was not the lesion itself, but rather the surrounding healthy brain tissue not yet affected by the tumor. Because of this, we excluded all areas within our isodose VOIs from measurement, which did not show a "normal" signal either in the original T2 images or the MD maps. Thus, we avoided the inclusion of pre-existing areas of edema or gliosis as well as of iron deposits or abnormally large feeding arteries or draining veins in case of vascular lesions. In order to concentrate on changes not due to a typical "adverse reaction" [22], we excluded all lesions where we expected a change of size after GK radiosurgery. Tumors with an expected change of size such as metastases or lymphomas as well as all cases with an apparent increase of enhancement or development of edema after treatment.

Having excluded all those changes which are obvious on routine MR imaging, we were confined to what some authors call "micro-structural alterations" [2] and their effect on DTI parameters. Mainly RD has been shown to correlate well with fiber myelination and coherence [26] and DTI parameters are generally regarded as a measure of white matter integrity. So it is not surprising that this methodology has been applied repeatedly to measure radiation-induced changes of the white matter.

After the feasibility study [14], DTI parameters were recorded in long-term survivors treated successfully for posterior fossa medulloblastomas [13] or childhood leukemia [7] by cranio-spinal or whole-head radiation and additional chemotherapy, and the authors found a reduction in FA or MD even more than 20 years after treatment. A similar reduction in FA values in the temporal lobe was reported after radiotherapy of naso-pharyngeal carcinomas which was more pronounced during the early months after treatment [28]. In the normal-appearing brainstem, recovery of a transient reduction of FA was observed some years after cranio-spinal radiation of different childhood brain tumors. But not all patients, who had received the conventionally agreed brainstem tolerance dose of 54 Gy using conventional fractionated radiotherapy, got back to normalcy [11]. Some recovery of white matter tract damage, although finally being transient only, has also been observed 7 months after GK radiosurgery of an infratentorial AVM [30]. In addition, our data showed a significant correlation to the length of the time interval between GK radiosurgery and follow-up. However, this correlation was positive in the sense that the longer the time interval, the higher was the increase in MD and RD values, mainly in the 15–10 Gy VOIs. Because of our rather coarse time frame with measurement intervals of sometimes more than 1 year, we might have missed some of the transient changes mentioned earlier. There might also be later changes in parameters which we missed due to our rather short follow-up time of 9.6 months because in AVMs, vessel occlusions are known to progress for more than 2 years [15].

Outside the lesion, there was no significant correlation between the change of DTI parameter value differences and the margin dose applied to the lesion. Comparing paired white matter areas in the irradiated and nonirradiated hemisphere in a retrospective study of various intracranial tumors several years after treatment, Ravn et al. [20] reported an increase in the apparent diffusion coefficient (ADC) values reaching significance in the white matter areas, which had received a single-fraction margin dose of 15 Gy or more. In another study 2 months after stereotactic radiosurgery of 15 patients with gliomas, however, no significant change in ADC values was seen in the white matter volumes treated with a margin dose of 12 Gy or more, whereas FA was reduced as well as the number of fibers which could be tracked from these areas [5]. In addition, according to a chemoradiotherapeutic report [4], there is a high probability that stereotactic radiosurgery could change the DTI parameters in affected perilesional brain areas as compressed cerebral or cerebellar cortex, brainstem, and white matter tracts to a different degree depending on their anatomic localization. This, however, was not addressed in the present study.

Although we did not see a significant correlation in the DTI parameter changes to the margin dose applied to the

lesion, reductions in MD and RD were more pronounced in the 15–10 Gy than in the 10–5 Gy isodose VOIs. But do these changes really signify radiation-induced alterations of "white matter integrity"? In addition to having received a higher radiation dose, the 15–10 Gy VOI has a closer spatial relation to the lesion border. And because only the changes of MD and RD increased with the dose applied to these areas, but not the reduction of FA, other factors apart from the radiation itself may have been involved.

One may be the heterogeneity of brain structures surrounding the 50% isodose lines as intracerebral white matter, compressed cerebral or cerebellar cortex or brainstem tissue, which have been shown to react differently to radiosurgery as mentioned earlier [4]. In case of AVMs, the effects of the progressive occlusion of feeders and draining veins are not confined to the nidus itself, but may extend to the surrounding tissue by changing local perfusion and cerebral blood volume. A reduction in peri-target perfusion has been demonstrated after radiosurgery of AVMs and of tumors [23]. How far this could influence the measurement of DTI parameters is not well known. In kidneys, a positive correlation of MD and FA to blood flow has been demonstrated [9].

In irradiated tumors, radionecrosis and endothelial lesions [1] may induce infiltration of the perilesional areas by water, cytokines, and other products inducing a subtle interstitial edema not visible in MR imaging. This may explain the greater changes of MD as compared to FA because by our method, diffusion is measured predominantly in this space. In case of severe damage of the myelinated axonal sheaths, FA should have been affected to a larger extent as for example after stereotactic radiation of the trigeminal nerve [10].

Conclusion

We were able to demonstrate some changes in DTI parameters in the perilesional white matter after stereotactic GK radiosurgery increasing with the time interval after treatment. However, we cannot be sure to what extent these changes are in fact due to radiation-induced demyelination and to what extent other factors such as alterations of cerebral perfusion or subtle perilesional edema not evident on structural MR, are involved. Follow-up studies of individual groups of lesions and the application of a strict timeframe are needed to see if these findings increase with time or they are just transient, and what other factors apart from direct radiation to the perilesional tissue are involved.

Disclosure: The authors have nothing to disclose and no conflict of interest.

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The authors stated that there are no conflicts of interest regarding the publication of this article.