Diffusion tensor imaging in glioblastoma patients treated with volumetric modulated arc radiotherapy: a longitudinal study

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\textbf{ABSTRACT}

\textbf{Background:} Chemo- and radiotherapy (RT) is standard treatment for patients with high-grade glioma, but may cause side-effects on the patient’s cognitive function.

\textbf{Aim:} Use of diffusion tensor imaging (DTI) to investigate the longitudinal changes in normal-appearing tissue in glioblastoma patients undergoing modern arc-based RT with volumetric modulated arc therapy (VMAT) or helical tomotherapy.

\textbf{Materials and methods:} The study included 27 patients newly diagnosed with glioblastoma and planned for VMAT or tomotherapy. All subjects underwent magnetic resonance imaging at the start of RT and at week 3, 6, 15, and 26. Fourteen subjects were additionally imaged at week 52. The DTI data were co-registered to the dose distribution maps. Longitudinal changes in fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were assessed in the corpus callosum, the centrum semiovale, the hippocampus, and the amygdala.

\textbf{Results:} Significant longitudinal changes in FA, MD, and RD were mainly found in the corpus callosum. In the other examined brain structures, only sparse and transient changes were seen. No consistent correlations were found between biodose, age, or gender and changes in DTI parameters.

\textbf{Conclusion:} Longitudinal changes in MD, FA, and RD were observed but only in a limited number of brain structures and the changes were smaller than expected from literature. The results suggest that modern, arc-based RT may have less negative effect on normal-appearing parts of the brain tissue up to 12 months after radiotherapy.

\section*{Introduction}

Postoperative radiotherapy (RT) constitutes a crucial part of the treatment against glioblastoma [1]. As standard therapy according to the Stupp protocol, surgery is followed by RT and concomitant chemotherapy with temozolomide (TMZ) starting approximately 4 weeks postoperatively [2,3]. However, irradiation is not harmless to the brain. RT-induced injuries are divided into three categories: acute reaction, early delayed reaction, and late delayed reaction. Acute reactions occur within days to weeks after the start of RT, early delayed reactions within 1–6 months after RT and late delayed 6 months to years after RT [4–6]. The acute and early delayed reactions can vary from mild to severe, with initial signs of vascular injury with endothelial damage, later subacute demyelination may occur [6], but both are generally considered to resolve spontaneously. In contrast, the late delayed reactions are irreversible and progressive and mainly affect the white matter as focal or diffuse damages, vascular changes, or radiation necrosis [7,8]. High RT dose, large volume, and the size of the fraction dose increase the risk of late neurotoxicity and can lead to a decrease in cognitive scoring [9,10]. Previous studies have, however, demonstrated long-term effects of RT also after a fraction dose below 2 Gy on cognitive functioning, compared to long-term survivors without RT, although a fraction dose below 2 Gy was primary expected to be safe [11]. Changes in different parts of the corpus callosum may appear early in Alzheimer’s disease before cognitive deficits [12]; the corpus callosum is also one of the white matter structures described to be sensitive to radiation-induced brain injury [6,13–16] and due to its central location often target of high RT dose.

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Different structures within the limbic system, for example hippocampus and amygdala, are involved in memory, cognitive and emotional functions. Several studies have shown that hippocampus appears especially susceptible to radiation damage [15–17], less studied is the radiation effect on the amygdala [18,19].

Lately new RT techniques have been developed, aimed at sparing the brain around the tumor and organs at risk (OAR) from radiation. Examples include volumetric-modulated arc therapy (VMAT) and helical tomotherapy. These new arc-based rotation radiation techniques can achieve highly conformal dose distributions with improved target volume coverage, thereby sparing non-tumorous normal-appearing brain tissue compared with earlier established RT techniques such as three-dimensional conformal radiotherapy (3D-CRT) [20]. Arc-based therapy may offer more favorable OAR sparing and in addition, a reduced treatment-delivery time compared with other newer techniques, such as intensity-modulated radiotherapy (IMRT) [20]. The clinical use of arc-based therapy methods is steadily increasing. Currently, the majority of published studies on arc-based therapy have focused on planning and feasibility [21,22], although there is emerging clinical outcome data concerning brain metastasis treatment [23,24].

It remains an open question whether arc-based RT reduces the damage to the white matter of the brain and in particular to structures relevant to the memory, such as corpus callosum and the limbic system. Damage to the brain, especially to the white matter can be assessed by diffusion tensor imaging (DTI) [25–28]. DTI provides two primary metrics. The first is the fractional anisotropy (FA) which reflects fiber density and coherence and tends to decrease in the case of damage to the white matter [25,29]. The second is the mean diffusivity (MD) [30,31], which is the average apparent diffusion coefficients across directions and is negatively correlated with cell density and positively correlated with the presence of edema and white matter degeneration. Previous studies have demonstrated a decrease in FA in some white matter structures after RT and this decrease was correlated with neurotoxicity in long-term survivors and decrease in the mean diffusivity (MD) [30,31], which is the average apparent diffusion coefficients across directions and is negatively correlated with cell density and positively correlated with the presence of edema and white matter degeneration. Previous studies have demonstrated a decrease in FA in some white matter structures after RT and this decrease was correlated with neurotoxicity in long-term survivors and predicted decreased cognitive function (intelligence quotient) [32]. Recent findings indicated that a decreased FA in the hippocampus precedes cognitive decline after RT [33] and a RT dose-dependent decrease of FA in some additional structures. An increase of MD in white matter fiber tracts of the limbic circuit has also been observed after RT [16]. In addition to FA and MD, DTI also provides the radial diffusivity (RD) and the axial diffusivity (AD), which reflect the diffusivity perpendicular and parallel to the main direction of the diffusion tensor, respectively. After RT, by examining the parahippocampal cingulum, an early increase in RD and decrease in AD could be seen, which correlated with late decline in verbal recall scores, verbal memory, and verbal fluency [14,34].

The aim of this study was to investigate the longitudinal changes in normal appearing brain tissue during and after modern arc-based RT methods, such as VMAT and tomotherapy, in a cohort of patients with glioblastoma WHO grade IV.

Materials and methods

Patients and RT

This prospective longitudinal study on high-grade gliomas used advanced brain tumor imaging. Inclusion criteria were patients newly diagnosed with glioblastoma WHO grade IV [36,37] planned for standard postoperative radio-chemotherapy according to the Stupp protocol [2]. Twenty-seven patients with a median age of 58 years met the criteria and accepted participation. All patients received concomitant chemotherapy with TMZ (75 mg/m²) during RT, followed by adjuvant TMZ 150–200 mg/m² 3–6 cycles depending on clinical response. RT was given according to the Swedish national guidelines for RT of glioblastoma, the most recent version of these guidelines is found in this link: Hjärtumtömrör – RCC Kunskapsbanken (cancercentrum.se), including reference to ICRO reports numbers 50, 62, 83, and 91 [38].

The prescribed dose was 60 Gy in 2 Gy fractions, given daily 5 days a week. Target was defined on dose planning MRI, where gross tumor volume encompassed contrast enhancing tumor on T1, operation cavity, unambiguous low-grade tumor on T2/FLAIR but not tumor edema; isotropic expansion to clinical target volume (CTV) with 2 cm, adjusted for natural barriers. Risk organs and respective maximum doses were defined according to the national guidelines. Treatment was given with VMAT or tomotherapy. RT plans were normalized so the 95% isodose line encompassed the planning target volume completely, except when dose to risk organs (optic chiasm, brain stem) were prioritized over CTV coverage. Clinical and demographic data for each patient are presented in Supplemental Table S1.

The study protocol included MRI at predefined timepoints where each patient performed MRI examinations immediately at start of RT (baseline week 0) and at 3, 6, 15, and 26 weeks after the onset of RT. Fourteen patients were additionally examined at week 52.

The corresponding biological equivalent radiation dose (biodose) for each structure was calculated as:

$$E_{Q2} = D\left(\frac{d + \alpha/\beta}{2 + \alpha/\beta}\right)$$

where D is the total dose, d is the fraction dose, and $\alpha$ and $\beta$ are organ- and endpoint-specific constants [39].

The study has been approved by the ethical committee prior to inclusion of patients (#2011/598, 2011/14, 2012/188, 2014/368). All patients have given informed consent prior to being included in the study according to recommendations of the Helsinki Declaration of the World Medical Association.
MRI of the brain was performed on a Magnetom Skyra 3 T system (Siemens Healthcare, Erlangen, Germany). The MRI protocol consisted of morphological imaging; T2W-TSE (TE/TR = 100 ms/6870 ms), T2W-FLAIR (TE/TR/TI = 81 ms/9000 ms/2500 ms) and T1W-MPRAGE (TE/TR/TI = 2.54 ms/1900 ms/900 ms, 1 mm isotropic voxels). The MPRAGE-sequence was performed before and after intravenous contrast administration of 0.2 mL/kg of Gadolinium-DOTA (Dotarem®, Gothia Medical/Guerbet). Diffusion-weighted images (DWIs) were acquired using 30 diffusion-encoded directions with a b-value of 1000 s/mm² and a 2 mm isotropic resolution.

MRI post processing

The DWI were corrected for subject motion and eddy current artifacts using Elastix [40,41]. No large motions were found, as the mean (STD) root-mean-square displacement was 0.5 (0.32) mm and the mean (std) root-mean-square rotation around the x-axis was 0.7 (0.29) degrees. All MR-images were co-registered to the MPRAGE images. DTI was performed to compute RD, AD, MD, and FA using an in-house developed Matlab-based software. The CT treatment plans and the corresponding dose distribution maps were co-registered to the baseline T1-MPRAGE image, using Elastix with rigid body transformations.

All DWIs underwent a manual quality analysis, where acquisitions were judged as either fail, check, or pass. Fail indicates an acquisition corrupted due to e.g. severe motion artifacts, check that an extra review was needed, and pass that the acquisition was of high quality. Here, an acquisition refers to all DWIs of one subject at one time point. No acquisitions were flagged as ‘failed’, but three acquisitions rendered a ‘check’. Out of these, two showed a single DWI affected by an RF-spike; however, these were in the most inferior or superior slices meaning the ROIs were not affected. The third subject showed reduced signal in three slices; however, this had no discernable effect on DTI parameter maps. These three acquisitions were therefore included in the subsequent analysis.

Selection of region of interest

DTI parameters in different normal-appearing structures were analyzed after defining regions of interest (ROI) in homogenous tissue. Three different structures of the corpus callosum were examined: splenium, corpus, and genu. In each of these structures, a ROI of 50 voxels was placed, which equals 0.05 cm³. The structures were contoured on the directionally encoded color-map using the baseline-examination and manually confirmed. If needed, manual adjustments were performed, on the subsequent scans (Figure 1). Normal-appearing white matter in the centrum semiovale in the right hemisphere was contoured on the T1-weighted image. The ROIs in this structure comprised 350–545 voxels, which equals 0.35–0.545 cm³. The hippocampus and amygdala were contoured bilaterally on the T1-weighted image and manually adjusted, to exclude partial volume effects, using the MD map. The ROIs in these structures comprised 300–640 voxels and 80–120 voxels respectively, which equals to 0.30–0.64 cm³ and 0.08–0.12 cm³, respectively (Figure 1). DTI measurements were excluded from the analysis when edema and/or tumor infiltration seemed to have a direct effect of the structural integrity of a specific ROI. This was determined by manual inspection of all acquired images.

Statistical analysis

To assess the longitudinal DTI findings from the predefined time points as change from baseline at the specific time points; changes in FA, MD, RD, and AD, a linear mixed-effects model was fitted to the respective parameter values from each brain region, given by

\[ Y_{ij} = \beta_0 + \beta_{1i} + \psi_j + e_{ij}. \] (2)

The dependent variable \( Y_{ij} \) was the ROI-average parameter value at time point \( i \) for subject \( j \). The fixed effects comprised the baseline average \( \beta_0 = (Y_{0j}) \) as well as the average differences from the baseline at each time point \( \beta_{1i} = (Y_{ij} - Y_{0j}) \), where \( \langle \cdot \rangle \) averages across subjects. The random effects comprised the random intercepts \( \psi_j \) for subject \( j \) as well as the random errors \( e_{ij} \), assumed to be normally distributed with zero mean and the standard deviations \( \sigma_{\text{subject}} \) and \( \sigma_{\text{error}} \), respectively. Thus, the five variables of interest were the average differences from the baseline at weeks 3 to 52, given by \( \beta_{1i} \) for \( i = 2 \ldots 6 \). \( \beta_{10} \) (trivially equals 0). In the analysis, for any given parameter and structure, subjects contributing data from fewer than four time points were excluded, and so were data points that differed by three or more mean average deviations from the median.

To assess the impact of biodose and age on the change in diffusion parameters, Pearson correlation analyses were performed for each parameter, structure, and time point. Furthermore, the impact of gender was assessed by performing t-tests between the male and female subjects for each parameter, structure, and time point. In each analysis, results for which \( p < 0.01 \) were considered significant.

No corrections for multiple comparisons were applied. For details on data exclusion and the number of subjects included in each analysis, see Supplemental Tables S5–S8.

Results

Clinical and demographic characteristics of the patients are presented in Supplemental Table S1. Twenty-seven patients, 17 males and 10 females, with a median age of 58 years and an age range of 34–71 years, who met the inclusion criteria and accepted participation were enrolled. Fourteen patients had tumors located in the left and eleven in the right hemispheres. Two patients had multifocal glioblastoma involving the corpus callosum. Each patient underwent surgery, either resection (22 patients) or biopsy (5 patients), and postoperative RT using volumetric-modulated arc therapy (VMAT; 16/27) or tomotherapy (11/27). Twenty-six patients received
treatment according to standard Stupp regiment [2]: radiation with 60 Gy in 30 fractions. One patient received 34 Gy in 10 fractions due to tumor properties. Each patient received concomitant chemotherapy with TMZ during RT, followed by adjuvant TMZ. The median progression-free survival was 9 months (range 5–30 months). Three patients were alive at the end of the study time (Supplemental Table S1). The mean radiation dose received to analyzed structures and the calculated corresponding mean biodoses are presented in Table 1, range for mean accumulated radiation dose and calculated biodose 20–39 Gy and 16–35 Gy, respectively depending on structure. For details of the dose distribution, see Tables 1 and 2.

An example of the longitudinal MRI data is shown in Figure 2. The longitudinal diffusion changes analyzed by the mixed model are presented in Table 2. Significant DTI changes from baseline were in general limited to the corpus callosum. In the genu, the RD was increased at week 15 (0.02 μm²/ms) and week 52 (0.03 μm²/ms), with a concomitant decrease in the FA (~0.02 and ~0.03, respectively). In the body, the RD was increased at all time points (between 0.03 and 0.04 μm²/ms), with a concomitant increase in MD between weeks 6 and 52 (0.03 μm²/ms) and decrease in FA at week 3 (~0.02), week 6 (~0.02), and week 15 (~0.03). In the splenium, the MD was decreased at week 52 (~0.04 μm²/ms). In the right centrum semiovale and in the right hippocampus, significant changes were seen only at week 26, with decreases in RD (~0.03 μm²/ms and ~0.02 μm²/ms, respectively) and MD (~0.02 and ~0.02 μm²/ms, respectively). In the left hippocampus and in the amygdala, no significant DTI changes were seen.

The Pearson correlation coefficients between changes in the different DTI parameters with biodose and age are shown in Supplemental Tables S2 and S3, respectively, for each structure and time point. Significant biodose correlation to DTI parameter change was only observed as a positive correlation between FA change in the right amygdala at week 15 (r = 0.58) and a negative correlation between AD change in the body of the corpus callosum at week 15 (r = −0.54; p < .01). No significant correlations were seen between changes in DTI parameters and age.

| Structure                  | Dose       | SD       | Range | Biodose | SD       | Range |
|----------------------------|------------|----------|-------|---------|----------|-------|
| Genu                       | 26.6 ±16.3 | 1.5–58.8 | 21.9 ±17.1 | 1.0–58.6 |
| Corpus                     | 34.1 ±17.8 | 1.2–60.6 | 29.8 ±18.7 | 1.0–60.6 |
| Splenium                   | 38.8 ±18.7 | 4.0–60.6 | 35.2 ±20.7 | 2.0–60.6 |
| Right centrum semiovale    | 28.2 ±15.4 | 1.0–60.0 | 23.5 ±15.4 | 1.0–60.0 |
| Right hippocampus          | 23.0 ±21.1 | 1.0–60.2 | 20.1 ±25.1 | 1.0–60.2 |
| Left hippocampus           | 24.5 ±20.7 | 1.4–60.3 | 21.3 ±21.3 | 1.0–60.2 |
| Right amygdala             | 19.6 ±18.4 | 1.9–60.5 | 16.1 ±18.4 | 1.0–60.5 |
| Left amygdala              | 20.3 ±18.6 | 2.0–61.1 | 17.0 ±18.5 | 1.0–61.2 |

Figure 1. (A) The corpus callosum on a FA-color map. The ROI placed within the structures from left: splenium, corpus and genu, viewed at a sagittal view. (B) The centrum semiovale in the right hemisphere on a post contrast T1-weighted image, viewed on the transversal plane. (C) The amygdala in the left hemisphere on a post contrast T1-weighted image, viewed on the transversal plane. (D) The left hippocampus on a post contrast T1-weighted image, viewed on the sagittal plane.
Table 2. Changes in diffusion parameters per structure at each predefined timepoint (w = weeks from baseline).

| Structure | FA [1]  | Biodose (Gy) | BL | 3 w | 6 w | 15 w | 26 w | 52 w |
|-----------|--------|--------------|----|-----|-----|------|------|------|
| CC genu   | 0.76 (0.06) | 19 (15) | 0.00 | −0.01 | −0.02** | −0.01 | −0.03*** |
| CC body   | 0.64 (0.05) | 30 (19) | −0.02** | −0.02** | −0.03*** | −0.02* | −0.02 |
| CC splenium | 0.79 (0.08) | 33 (20) | −0.01 | 0.00 | −0.01 | 0.01 | 0.01 |
| CSO right | 0.34 (0.05) | 22 (15) | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| HC left   | 0.15 (0.01) | 16 (19) | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| HC right  | 0.15 (0.01) | 17 (19) | 0.00 | 0.01* | 0.01 | 0.01* | 0.00 |
| AM left   | 0.15 (0.02) | 16 (19) | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| AM right  | 0.15 (0.02) | 17 (19) | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| MD (µm²/ms) |        |        | Change from baseline (BL) | | | | | |
| Structure | Biodose (Gy) | BL | 3 w | 6 w | 15 w | 26 w | 52 w |
| CC genu   | 0.71 (0.06) | 19 (15) | −0.01 | −0.01 | −0.01 | −0.02 | −0.04** |
| CC body   | 0.79 (0.05) | 30 (19) | −0.03** | −0.03*** | 0.03*** | 0.03*** | 0.03*** |
| CC splenium | 0.66 (0.07) | 33 (20) | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| CSO right | 0.78 (0.06) | 23 (16) | −0.01 | −0.01 | −0.01 | −0.02** | −0.01 |
| HC left   | 0.84 (0.02) | 18 (19) | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| HC right  | 0.85 (0.04) | 19 (20) | −0.01 | −0.01 | −0.01 | −0.02** | 0.00 |
| AM left   | 0.78 (0.04) | 16 (19) | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| AM right  | 0.77 (0.04) | 16 (19) | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| RD (µm²/ms) |        |        | Change from baseline (BL) | | | | | |
| Structure | Biodose (Gy) | BL | 3 w | 6 w | 15 w | 26 w | 52 w |
| CC genu   | 1.51 (0.09) | 22 (17) | −0.01 | −0.01 | −0.01 | −0.02 | −0.05* |
| CC body   | 1.49 (0.08) | 30 (19) | 0.01 | 0.01 | 0.01 | 0.02 | 0.03 |
| CC splenium | 1.44 (0.10) | 36 (21) | 0.01 | 0.01 | 0.01 | 0.02 | 0.05* |
| CSO right | 1.06 (0.06) | 22 (15) | −0.01 | −0.01 | −0.01 | −0.01 | −0.01 |
| HC left   | 0.97 (0.03) | 18 (19) | 0.00 | −0.01 | 0.00 | 0.00 | 0.00 |
| HC right  | 0.97 (0.04) | 18 (20) | −0.01 | −0.01 | −0.01 | −0.02* | 0.00 |
| AM left   | 0.90 (0.05) | 16 (19) | −0.01 | −0.01 | −0.01 | −0.02* | −0.01 |
| AM right  | 0.89 (0.04) | 16 (19) | 0.00 | 0.00 | 0.00 | −0.02 | 0.00 |

The values in the week columns are the coefficients estimated in the mixed-model analysis. No corrections for multiple comparisons were applied.

CC: corpus callosum; CSO: centrum semiovale; HC: hippocampus; AM: amygdala.

The CSO left was excluded from analysis due to tumor infiltration in a majority of cases.

*p < .05,
**p < .01,
***p < .001,
****p < .0001.

Biodose and BL values are given as mean (inter-subject SD).
The results of the t-tests comparing changes in DTI parameters between male and female subjects are shown in Supplemental Table S4 for each region and time point. In this material females exhibited larger changes to MD and AD in three structures: in the left hippocampus at week 6 (0.03 μm²/ms and 0.04 μm²/ms, respectively) and in the left amygdala at week 6 (0.04 μm²/ms and 0.05 μm²/ms, respectively) and in the genu of the corpus callosum at week 52 (0.08 and 0.15 μm²/ms, respectively).

Discussion

This prospective study used DTI in glioblastoma patients to investigate longitudinal changes in normal-appearing brain structures during and up to 12 months after irradiation with arc-based therapy. In general, the changes were very limited outside the corpus callosum. The most consistent effect was seen in the body of the corpus callosum in form of an increase in RD and MD and a decrease in FA—a pattern that typically suggests degenerative changes to white matter. The effect persisted at 12 months and is consistent with the body of the corpus callosum receiving a relatively high median biodose due to its central location (30 Gy, Table 1). The genu of the corpus callosum exhibited a similar pattern, although only at two timepoints and with no clear effect on the MD. In the other examined structures, however, significant effects were sparse, transient, and bidirectional, and were likely of limited biological relevance given the relatively large number of comparisons involved. This is in contradiction to previous studies of diffusion changes after RT. Previous studies have demonstrated comparatively larger effects in the corpus callosum [13,15,16,42] as well as changes throughout white matter [15,32,43]. In particular, large effects have been seen in limbic circuits associated with the hippocampus, such as the cingulum and the fornix [15,16,42,44] and in the hippocampus itself [33]. Also, the changes were generally not correlated with radiation dose or age (Supplemental Tables S2 and S3). Transiently, female gender correlated to larger AD and MD changes in the left hippocampus and amygdala (Supplemental Table S4). At week 26 DTI changes both increasing and decreasing were seen, depending on structure, similarly observed by Connor et al. [42].

There are several possible explanations for the relatively small effects on normal-appearing tissue observed in this study compared to previous reports. One is the difference in RT techniques. The treatment of tumors is in constant change and new improvements in surgery and RT are continuously being developed [22,45]. Since newly diagnosed patients receive new regimes, compared to those applied in previous studies, the effects we found might therefore not be entirely comparable to earlier studies. There are several aspects which could explain why the effects seem to be more modest in this material compared with previous studies, such as new radiation regimes, techniques such as VMAT and other arc-based therapies with better tissue-sparing treatments of sensitive regions such as the hippocampus. In the present study, arc-based rotation therapy was used in all 27 patients. This technique achieves optimized dose distribution with improved target volume coverage and is described to affect normal-appearing tissue less, compared to 3D-CRT [20]. This may indicate less neurotoxic effects of modernized arc-based RT in vulnerable structures such as hippocampus and corpus callosum. That interpretation is supported by recent result from the same study population, demonstrating unchanged cognitive function in neuro-cognitive testing at 1-year follow up [46]. However, these are indirect indications. We did not compare patients treated with arc-based RT with patients treated with earlier methods such as 3D-CRT or of IMRT. Note that during the study period, arc-based therapy became standard method of RT for glioma patients at the study site.

Another possible explanation for the small diffusion effects observed in this study are differences in the location of the tumors and the anatomical structures evaluated in our cohort compared with previous studies. In contrast to previous studies with a more heterogeneous patient cohort [14,34,47], the present study had a patient cohort with a more homogenous tumor histology as all were glioblastoma WHO grade IV. These high-grade tumors may be expected to have a more diffuse infiltrative growth pattern, which would affect the diffusion properties in adjacent tissue differently. Our selection of only high-grade glioma patients and the used radiation technique might have resulted in larger variation in radiation dosage to the different brain structures evaluated, compared with whole brain irradiation and other RT techniques [13–16,34,47]. It can always be brought to consideration weather DTI is a technique that can detect tissue changes due to RT in normal appearing brain. However, our findings can be supported by a few previous studies, in which effects were found in a portion of radiated structures, including hippocampus and corpus callosum, by using a very similar approach to ours [42–44,47].

The age of the patient could affect how the brain responds to irradiation. Exactly how DTI properties and the effect of irradiation might vary depending on age is somewhat unclear. The age of the patients ranged from 34 to 71 years, which is similar to several previous studies [13,16,34,43,44,47]. No statistically significant differences in measured values in relation to age were found in the present study, which is in contrast to some previous studies with focus on the effects of age on diffusion metrics, which demonstrated an age-related decrease in FA and an increase in RD [48,49]. One paper [47] observed age-related changes in AD and RD in white matter fiber bundles. Most of these studies were performed using different methods of irradiation, and a variation of underlying tumor types and grades.

Gender might be another confounding factor for changes in diffusivity due to irradiation [47]. In our study, sparse signs of differences between female and male patients were seen, with more change at the end of RT in MD and AD in the left hippocampus and in the left amygdala in females. Apart from that, no significant gender correlated effects were seen on diffusion parameters in any of evaluated structures up to 6 months. Whether gender affected measured parameters at 12 months from baseline is uncertain, due to few individuals examined.
We wish to highlight five limitations. First, we needed to excluded some of the measurements due to partial volume effects (the image voxels consisted of mixed tissue types) [50] and structural alterations of tissue, due to tumor infiltration and increased surrounding edema. Second, as in other DTI studies investigating patients with this rare diagnosis [14,34,43,47], this study has a patient cohort of limited size. On the other hand, the study was focused on patients with only the diagnosis glioblastoma WHO grade 4 and the number of patients were in range with earlier studies or higher. Third, we used a manual contouring method instead of more automatic analysis methods such as TBSS [15]. Single investigator contouring structures manually might result in selectively bias, and one might consider an automated program to be more objective. However, to reduce potential single investigator bias in our study, a senior neurroradiologist with 25 years of experience (PCS) reviewed the manual adjustment performed by the operator to ensure good ROI placement in the different structures. Fourth, a high number of statistical tests were performed. This increase the probability that some of the significant effects found were false positives. This could have been mitigated by reducing the significance threshold by performing a Bonferroni correction. However, this would have increased the false negative rate and simultaneously increasing the minimal detectable effect size. Here, we balanced the two competing interests but prioritized a low false negative rate by using 0.01 as the significance threshold. The number of significant findings was still limited, which supports the notion that the changes in our material were indeed small. Fifth, diffusion MRI is sensitive to the tissue microstructure, but also due to experimental artifacts such as signal dropout. However, the quality assessments did not indicate any quality-related problems.

Conclusion

The present study supports that modern RT results in limited longitudinal changes in the brain tissue as measured by FA, MD, RD, and AD. These findings suggest that irradiation using arc-based therapy may have less negative effect on the normal-appearing parts of the brain than previously has been reported for brain tumor patients treated with 3D-CRT.

Disclosure statement

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Data availability statement

All model fitting and statistical analyses were performed using MATLAB (R2019a, MathWorks, Natick, MA, USA) together with the multidimensional dMRI toolbox [51] Available: https://github.com/markus-nilsson/md-dmri, and Elastix.

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