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Short Communication

Retrospective assessment of MRI-based volumetric changes of normal tissues in glioma patients following radio(chemo)therapy

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ABSTRACT

In glioma patients, linac-based photon beam irradiation is a widely applied therapy, which achieves highly conformal target volume coverage, but is also known to cause side-effects to adjacent areas of healthy tissue. Apart from subjective measures, such as quality of life assessment and neurocognitive function tests, objective methods to quantify tissue damage are needed to assess this impact. Magnetic resonance imaging (MRI) is a well-established method for brain tumor diagnoses as well as assessing treatment response. In this study, we retrospectively assessed volumetric changes of gray matter (GM) and white matter (WM) in glioma patients following photon irradiation using a heterogeneous MRI-dataset obtained in routine clinical practice at different sites with imaging parameters and magnetic field strengths. We found a significant reduction in WM volume at one year ($p = 0.01$) and two years ($p = 0.008$) post radio(chemo)therapy whereas corresponding GM volumes did not change significantly ($p = 0.05$ and $p = 0.11$, respectively). More importantly, we also found large variations in the segmented tissue volumes caused by the heterogeneous MR data, thus potentially masking more subtle tissue changes over time. On the basis of these observations, we present suggestions regarding data acquisitions in future prospective MR studies to assess such volumetric changes.

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Introduction

Adjuvant radio(chemo)therapy is one of the cornerstones of treatment in low- and high-grade glioma patients [1–3]. However, it is well-established that radiotherapy (RT) leads to long-term side-effects of the healthy brain tissue, e.g., leukomalacia, tissue atrophy, vascular changes or changes of diffusion and perfusion [4–9]. Moreover, the influence of irradiation on cortex thinning and on cerebral blood flow in the GM has recently been reported [10,11]. There are several approaches to objectively measure the influence of radiation on normal tissue, e.g., anatomical changes assessed by tissue shrinkage. By means of T1-weighted MR scans and appropriate image processing it is possible to segment various

tissue types and calculate their partial volumes. With a repeatedly conducted examination, volumetric changes of specific tissue types can be determined over time and correlated to the patient's subjectively reported neurocognitive function using neurocognitive function tests. This approach is of particular interest to objectively assess cerebral volume changes after particle therapy, that, due to its distinct characteristics, reduces dose to normal tissue and is thus expected to lead to decreased normal tissue damage (e.g., ProtoChoice-Hirn, NCT02824731). In general, there are predefined protocols for acquisition (e.g., magnetic field strength and modalities) and imaging parameters (e.g., field of view, in-plane resolution, and slice thickness) of MRI scans that are obtained within clinical studies. In contrast to this, examinations acquired in clinical routine for diagnostics and follow-up as suggested also from Weller et al. [12] are executed according to institutions protocols without uniform imaging characteristics. In spite of their heterogeneity, clinical data have one major benefit compared to well-designed trial data: they are already available in large

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quantities serving as valuable source for retrospective analyses. Therefore, in this study we assessed whether anatomical MRI scans obtained in clinical routine were able to depict volumetric changes of normal tissue after photon-based radio(chemo)therapy.

Materials and methods

Subjects

This retrospective analysis of longitudinally obtained data was performed on data within the clinical picture archiving and communication system (PACS) of University Hospital Carl Gustav Carus Dresden, Germany, with consent of the local Medical Ethics Committee. In total, MR datasets of 84 patients with WHO grade II and III glioma who had undergone adjuvant radio(chemo)therapy after tumor biopsy, subtotal or gross tumor resection were available. After selecting those individuals having an unambiguous primary tumor position (right or left, not affecting both hemispheres) and undergoing high dose RT (total dose $D > 54$ Gy), 26 patients (17 male and 9 female) remained for further analysis (Table 1).

Data

Structural MR-scans (T1-weighted modality without contrast medium) were acquired in the interval between surgery and initiation of radio(chemo)therapy serving for radiation treatment planning purposes, and at several time points thereafter. Even though the imaging intervals were set in local treatment protocols, in clinical routine they varied considerably ranging from weeks to several months. MR scans were acquired at various outpatient or hospital-based institutions. Consequently, data was acquired at different field strengths (1.5 T for majority of scans, 3 T for approx. 20%), using scanners from different vendors (Siemens Healthineers: 65%, GE Healthcare: 28%, and Philips Healthcare: 7%), and conducting different MR sequences. On average each patient underwent 9 MRI examinations thus resulting in a total of 259 scans to be analyzed.

Image processing

We developed an image-processing pipeline to process these images with heterogeneous geometrical characteristics for normal tissue volume calculations (Suppl. Fig. 1). First, all T1-weighted images were bias field corrected using N4ITK [13] and aligned to the average MNI152 brain atlas using rigid body co-registration as well as reslicing using trilinear interpolation implemented in FSL/FLIRT [14,15]. The resulting T1w images in the MNI space were segmented into GM, WM and cerebrospinal fluid (CSF) using SPM12 (Statistical parametric mapping toolbox for MATLAB

Table 1
Patient and scan characteristics.

Characteristic	Value
Gender (male/female)	17/9
Age in years (min/median/max)	24/48/74
Scans per patient (min/median/max)	2/9.5/25
Voxel volume in mm³ (min/median/max)	0.24/1.19/5.98
Magnetic field strength in T	
1.5	200
3.0	59
Manufacturer	
Siemens Healthineers	169
GE Healthcare	72
Philips Healthcare	18

version 9.0 from The MathWorks, Inc., Natick, MA) [16–18]. After segmentation, the total volume of each of the three tissue classes was calculated. The subsequent intersection with a modified right/left labeled hemisphere mask (cerebellum excluded) resulted in the definite tissue volume to exclude the hemisphere from analysis containing the brain tumor.

Data analysis

In order to compare the segmented tissue volumes in the contralateral hemisphere over time, they were scaled according to their voxel size within the individual patient's time series. Subsequently, these partial volumes V were normalized using the T1-weighted MR scan before initiation of radio(chemo)therapy as baseline V_{BL} to $\tilde{V} = \frac{V}{V_{BL}} - 1$ such that 0 represented a constant partial volume, positive values indicated an increased partial volume, and negative values reflected a partial volume decline. Next, a linear regression was calculated in order to depict the averaged trend of partial volume changes. In addition, all data were time shifted in accordance with their particular timestamp of RT. Hence the time scaling for each patient was normalized and started at zero with the last MRI scan previous to RT, to allow for comparability within the cohort. The measurements after RT were discretized in time slots of three months each, with box plots representing the distribution of volumetric changes over time. In order to assess the significance of long term changes of partial tissue volumes (whole brain, GM, and WM) a two-sided Wilcoxon signed-rank test was calculated and a $p \leqslant 0.05$ considered statistically significant (SPSS Statistics Version 23, IBM, Ehningen, Germany [19]).

Results

With the implemented image processing pipeline it was possible to normalize the heterogeneous MR-data (bias field correction and registration to MNI space) and segment GM, WM and CSF in all patients. Fig. 1 shows an example of the segmentation result with an axial in-plan voxel spacing 0.98 mm × 0.98 mm and slice thickness in z direction of 5 mm with a slice gap of 0.5 mm. The quality of segmented volumes (depicted in blue) differed depending on the plane visualized: while in the axial plane they were depicted in high detail, in the coronal and sagittal views they were shown at low resolution.

Suppl. Fig. 2 shows the longitudinal series $(t_1, \ldots t_4)$ of T1-weighted MRI scans and their corresponding histograms of the three tissue classes (GM, WM, and CSF) of an exemplary patient. As can be gathered from the histograms, we found varying intensity levels for the three tissues in these T1 weighted scans, which is caused by the diverse imaging parameters used in routine outpatient clinics. Hence, an intensity-based assessment was not found to be feasible.

Time-dependent changes were subsequently analyzed in the segmented tissue volumes and assessed using linear regression (Suppl. Fig. 3(a)). At two time-points, the volumetric measurements deviated from the expectation, for the patient underwent T1-weighted MRI with a divergent magnetic field strength and image resolution (Suppl. Fig. 3(b)). Consequently, the linear regression of the CSF curve had an implausible positive slope. After filtering the outliers, the positive trend for CSF increase vanished but the negative trend for GM and WM volume remained. Such discontinuous effects based on different modalities and resolutions were detected in all patients during longitudinal analyses. Finally, Fig. 2 illustrates the assessment of the total cohort with regard to the volumetric changes of GM, WM, and the whole brain over a two-year period. As can be appreciated, most data were available one year after RT, whereas after two years, data for approximately half
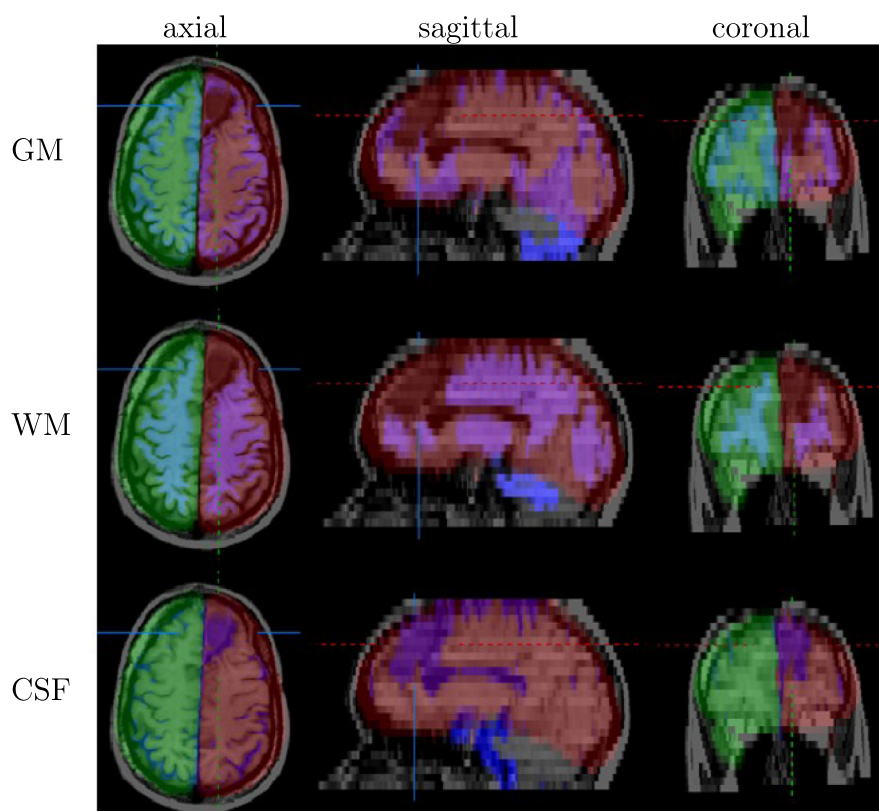
Fig. 1. Axial, sagittal and coronal planes of MRI volume through a glioma within the left frontal lobe with tissue segmentation (green/red: right/left brain mask excluding cerebellum and brainstem, blue: segmented tissue class [GM/WM/CSF]). (For interpretation of the references to colour in this figure caption, the reader is referred to the web version of this article.)

of the patients was available. The follow up scans were applied at irregular intervals which leads to different compositions of patient groups per quarter. While on average the entire brain volume (GM + WM) remained constant two years after completion of radio (chemo)therapy ($p_t \gg 0.05$ with $t = 3 \ldots 24$ months), the segmented volume of GM and WM varied quite considerably both within the total cohort and within the individual patients. At one and two years after completion of radio(chemo)therapy, the WM volume decreased significantly ($p = 0.01$ and $p = 0.008$, respectively), whereas as no significant change in GM volume was detected, neither after one year ($p = 0.05$) nor after two years of follow-up ($p = 0.11$).

Discussion

Quantification of volumetric tissue changes after RT by means of MRI assessment is a promising approach to generate objective measures of radiation side-effects. However, inconsistency within retrospective data sets (imaging parameters, resolution or magnetic field strength) leads to high variability in volumetric measurements. Differences in MRI resolution bias such volume measurements due to different degrees of the partial volume effects between the tissue types. Equally, offsets in tissue contrasts caused by differences in T1w weighting due to the use of various MR sequences, imaging parameters and magnetic field strengths will particularly bias the separation of WM and GM.

We found a significant reduction in WM volume one and two years after completion of radio(chemo)therapy, and no significant change in GM volume neither one nor two years after RT. In contrast to this, Purst et al. [10] found a decrease in total brain volume and GM (of approx. 2%), but no significant change in WM volume in 14 patients with glioblastoma receiving photon-based RT and

temozolomide. Petr et al. [20] recently discovered a significant shrinkage of both GM (2%) and WM (1.3–2.3%) volume after photon-based therapy in 43 patients. Karunamuni et al. [7] investigated the impact of fractionated RT on cortical matter of 15 high-grade glioma patients. After one year they found significant cortical thinning (-0.0033 mm for every 1-Gy increase in RT dose). The common ground of the aforementioned works is a well-defined cohort as well as a detailed defined image acquisition protocol for scan resolution and follow-up intervals. The discrepancy of our findings with those reported in the literature may be caused by different patients characteristics, different treatments (RT dose or concurrent/adjuvant chemotherapy, the latter not completely assessable in our cohort), or heterogeneous MR data in our retrospective analysis potentially masking small volumetric tissue changes over time. Consequently, this study shows the importance of exact MR protocols in treatment preparation and during follow-up enabling quantitative evaluation of structural brain changes after radio(chemo)therapy. Together with the data on interpatient heterogeneity, our findings allow to design a prospective study using more consistent MR data acquisition in a clinical setting in patients treated with photon- or particle-based radio(chemo)therapy in order to assess the dependence of MRI-detected volumetric changes with delivered dose and possibly neurocognitive function tests.

This work points out the difficulties of retrospectively analyzing data acquired in clinical routine due to differences in acquisition parameters and in examination intervals. As a consequence of the results presented above, we propose minimum requirements about acquisition, completeness, and resolution for MRI based examinations.

MRI-based examinations should be performed with the same imaging specifications; in particular the magnetic field strength
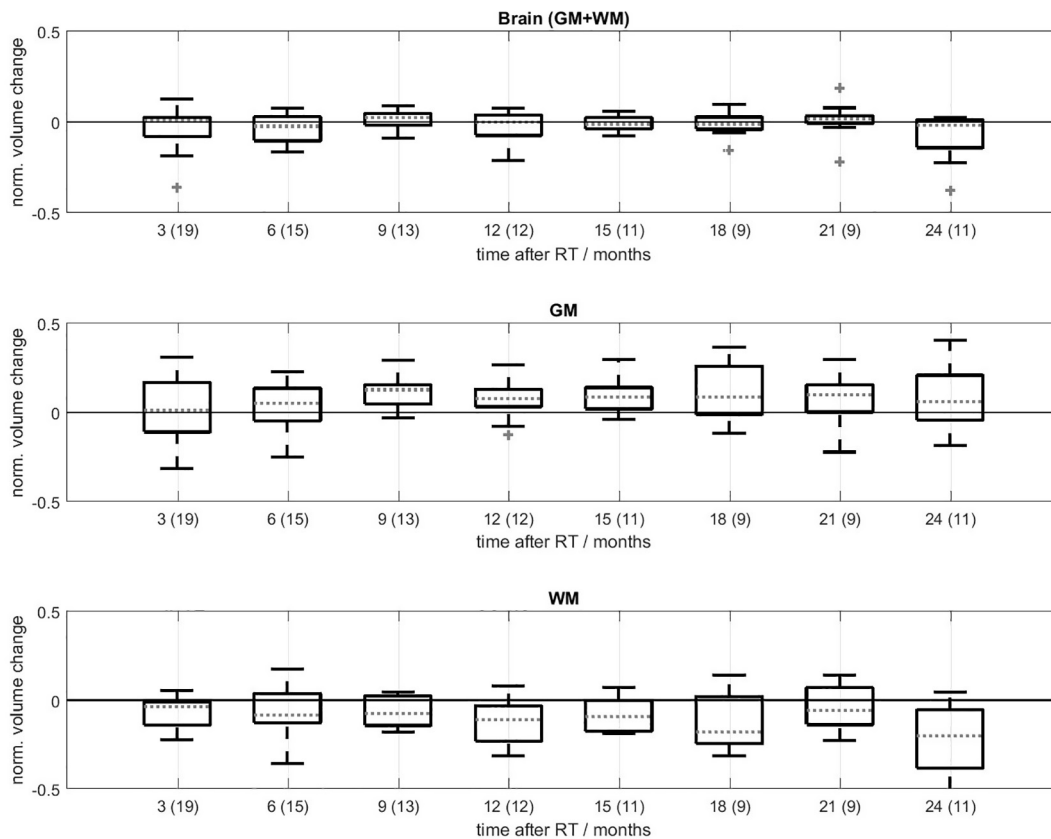
Fig. 2. Box plots of the MRI-based retrospective assessment of entire brain volume (upper row), gray matter (GM; middle row) and white matter (WM; lower row) in patients with grade II-III glioma over the course of two years after radiotherapy. The median values are highlighted in gray, the number of available data points in brackets.

ought to be unvaried. Furthermore most of the registration and segmentation algorithms assume an uncropped brain model. MRI scans incompletely depicting the brain lead to erroneous segmentation of tissue types. Volume calculations also require a complete MRI scan taking into account slice thickness and slice gaps in 2D MR sequences. Therefore a complete MRI scan is necessary. The same spatial resolution in MR scans facilitates the comparability of partial tissue volumes resulting from image processing without interpolation. For differentiation between GM and WM a high resolution is of particular interest for they contain small-sized geometric structures. An isotropic scan resolution with voxel size $V \leqslant 1$ mm^3 is recommended.

In summary, the retrospective volumetric analysis of heterogeneous MR data obtained in clinical routine is not recommended when searching for objective measures comparing treatment modalities. Instead, prospective protocols according the mentioned minimum requirements should be implemented allowing for subsequent high-quality retrospective analysis of volumetric changes. Prospective studies that have implemented these methodological improvements should be conducted in order to find imaging biomarkers prior to or early into radio(chemo)therapy predictive of volume loss.

Conflict of interest

There is no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ctro.2017.11.008.

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