Radiotherapy and Oncology 207 (2025) 110873

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Gross tumor volume increase and need for adaptive radiotherapy in pediatric-type diffuse high-grade glioma of the midline structures

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ARTICLE INFO

Keywords:
Adaptive radiotherapy
Pediatric-type high-grade glioma
Pediatric brain tumors
MRI

ABSTRACT

Introduction: Current pediatric-type diffuse high-grade glioma radiotherapy protocols apply a 1.0 cm clinical target volume (CTV) margin around the gross tumor volume (GTV). However, in adults with glioblastoma, large variations in GTV are observed during radiotherapy. The study aimed to map the GTV variation during a 6-week course of radiotherapy using repeated MR-imaging and to evaluate the need for plan adaptation. Also, the relation between GTV increase and time to disease progression (TTP) was assessed.

Material and methods: Patients with newly diagnosed diffuse midline glioma or diffuse pediatric-type high-grade glioma of the midline structures undergoing a 6-week radiotherapy course, were eligible for inclusion. MRI scans were performed in the pre-treatment phase (MRI0), and at fraction 10 + 20 (rMRI10/rMRI20). On all scans, GTV was delineated. An increase was defined as a >5 % increase of GTV between scans. The need for treatment plan adaptation was based on dosimetric and visual criteria. GTV increase was compared to TTP.

Results: Twenty patients were eligible. In 12/20 patients, a GTV increase was observed at rMR10/rMR20, more specifically in 6/11 pontine and 6/9 non-pontine tumors. Combining dosimetric criteria and visual inspection, 20 plan adaptations in 14 patients were required. The TTP (range: 1.6–17.6 months) was not significantly different between the group with (median 8.1 months) versus without a GTV increase (median 7.6 months; p = 0.66).

Conclusion: Repeated imaging demonstrated a GTV increase in 60 % of patients and plan adaptation in 70 %. When applying CTV margins of 1.0 cm, plan adaptation is recommended to ensure adequate radiotherapy treatment.

Introduction

Pediatric-type diffuse high-grade glioma (pHGG), such as H3K27M-altered diffuse midline glioma (DMG) and diffuse pediatric-type high-grade glioma (DPHGG) [1] of the midline structures are highly malignant tumors with a dismal outcome for nearly all patients [2,3]. The tumor location and the diffuse nature of these gliomas limit resection or debulking. In addition, the efficacy of chemo- or immunotherapy is hampered by the blood–brain- and blood-tumor-barrier, inherent resistance mechanisms and the highly immunosuppressive tumor microenvironment [4–7]. Therefore, upfront radiotherapy with or without chemotherapy and the option to re-irradiate at progression remains the cornerstone of treatment for these brain tumors [8–13].

Historically, whole brain irradiation was controversially advocated for pHGG of the brainstem/midline structures [14]. However, lack of survival benefit, increased morbidity and a dominant pattern of failure

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https://doi.org/10.1016/j.radonc.2025.110873
Received 9 December 2024; Received in revised form 18 March 2025; Accepted 25 March 2025
Available online 31 March 2025

at the primary tumor site consequently resulted in the use of limited fields, typically with a 2.0 – 3.0 cm clinical target volume (CTV) expansion of the gross tumor volume (GTV) [15–17]. Since no tumor-control benefit of wider margins was recently demonstrated in a cohort of 60 patients, CTV margins of 1.0 cm around the gross tumor were recommended and are currently implemented in prospective pHGG studies [18]. This margin reduction may increase normal tissue tolerance, given the increasing use of re-irradiation [19].

On the other hand, it is well known that pHGGs with residual macroscopic tumor may clinically deteriorate during a 6-week course of radiotherapy, because of acute side-effects, pseudo-progression or true progression [20]. In a recent study which included adult patients with a glioblastoma and macroscopic tumor at onset of radiotherapy, a repeated MRI at fractions 10, 20, and 30 demonstrated large GTV variations even early-on during treatment [21]. In this study, which prescribed a 2.0 cm isotropic CTV expansion, dose coverage of the tumor was not compromised and therefore plan adaptation was not performed. To our knowledge, the evolution of the GTV during radiotherapy and the potential impact of recommending CTV margins of 1.0 cm on dose distributions has not been explored in pediatric patients.

The aim of the current study is to retrospectively map the extent of GTV variation by repeated MR-imaging at fraction 10 and 20 in a cohort of pediatric patients with high-grade glioma arising from the midline structures, and to evaluate the need for a radiotherapy plan adaptation based on target coverage. Also, the relation between GTV increase and time to disease progression will be assessed.

Methods and materials

Patients

Since March 2021, all pediatric patients (<18 years) with a newly diagnosed pHGG are treated in an offline adaptive protocol with a repeated MRI at fraction 10 and fraction 20. Exclusion criteria for current analyses were 1) no macroscopic residue visible on post-operative MRI, 2) the use of a hypo-fractionation regimen, 3) no MRI available at fraction 10 and/or fraction 20, 4) referral for proton therapy and/or 5) a brain tumor not originating from the midline structures (thalamic area, hypothalamus, pituitary and pineal gland, brainstem, cerebellar vermis, corpus callosum, fornix, anterior & posterior commissure, cingulate gyrus, septum pellucidum and stria terminalis). Relevant patient, tumor and treatment characteristics were collected including age at onset, sex, tumor location, extent and date of surgery, integrated histopathological diagnosis, radiotherapy timing and dose, concomitant treatment strategies including corticosteroid use, and follow-up data. The retrospective analysis was approved by the Princess Máxima Center Biobank and Data Access Committee (Institutional Review Board approval number: PMCLAB2024.564). The need for informed consent was waived since offline adaptive radiotherapy (ART) was a standard of care treatment modality.

MRI imaging

All patients underwent a brain MRI in the pre-treatment phase (MRI0). In addition, repeat MRIs at fraction 10 (rMRI10) and fraction 20 (rMRI20) were acquired. The repeat MRI examinations included axial 3D T2-FLAIR and axial 3D T1-weighted (T1W) MRI sequences on a 1.5 T MRI (Philips Ingenia, Philips Healthcare, Best, The Netherlands). 3D T2-FLAIR images were acquired with a slice thickness of 1.2 mm, slice spacing of 0.6 mm, a voxel size of 0.96 × 0.96 mm^2 and a 240 × 240 reconstruction matrix. 3D T1W were acquired with a reconstructed slice thickness of 1.0 mm, slice spacing of 0.5 mm, a voxel size of 0.48 × 0.48 mm^2 and a reconstruction matrix of 480 × 480.

Target volumes

The GTV was delineated by an experienced radiation oncologist based on abnormalities seen on T2-FLAIR and T1W [22]. The GTV was delineated on the diagnostic MRI (MRI0) and adapted based on changes visible on rMRI10 and rMRI20. The CTV was defined as the GTV with an isotropic margin of 1.0 cm to account for microscopic spread [18], and limited by anatomical boundaries (such as the skull, ventricles, falx, tentorium cerebelli). A planning target volume (PTV) margin of 0.2 cm was used. For this evaluation, all MRI0 and MRI10/MRI20 target volumes were checked by a second radiation oncologist and delineation was adapted according to consensus.

Treatment planning

Patients were treated with volumetric modulated arc therapy (VMAT). The total prescribed dose was 54.0 Gy in 30 fractions (1.8 Gy fraction dose). The target coverage was considered adequate when the dose to 98 % of the CTV received 95 % of the prescribed dose (D98% > 95 %) and the dose to 95 % of the PTV received 95 % of the prescribed dose (D95% > 95 %). The dose constraints to the organs-at-risk (OARs) were in accordance with international guidelines [23–28]. The quality of the radiotherapy plans at each time point was evaluated using the conformity number and the homogeneity index [29,30]. The treatment plan was delivered using daily online imaging on a CBCT-linac and using a 6D table to correct for translations and rotations.

Plan adaptation

During treatment, repeat MRIs (rMRI10 and rMRI20) were rigidly registered to the pCT and were used to evaluate the need for plan adaptation. This was based on 1) the dosimetric coverage of the adapted CTV and PTV and 2) a visual inspection. The dosimetric criterion for the CTV was D98% > 95 % and for the PTV D95% > 95 %. If the dosimetric criteria were not met for either CTV or PTV, a new plan was indicated. Replanning was performed on the initial pCT, with care of adapted delineation of potentially deformed OAR. The visual inspection of the CTV and PTV was a binary check; if the adapted CTV was not encompassed by the original PTV a new treatment plan was required. The respective fractions 11 or 21 and onwards were administered according to the adapted plan.

Statistical analysis

GTV (cm^3) was noted at the start of radiotherapy (MRI0) and at rMRI10 and rMRI20. Tumor volume increase was defined as an increase of the GTV of >5 % between two consecutive time points. The GTV increase was analyzed against time to progression (TTP). The TTP was defined as a clinical (neurologic) deterioration, and/or diagnosis of progression of the primary tumor on MRI, and/or the presence of new leptomeningeal metastases on MRI. Progression free survival estimates were calculated using Kaplan-Meier analysis. P-values between risk groups were obtained using the log rank test.

Results

From March 2021 to October 2023, 48 patients with newly diagnosed pHGG were diagnosed at the Princess Máxima Center for Pediatric Oncology. Twenty-eight patients did not meet the inclusion criteria for this evaluation. In total, 20 patients with a tumor of the midline structures were retained for further analysis (Fig. 1).

Patient, tumor and treatment characteristics are listed in Table 1. Median age at start of radiotherapy was 9.1 years (IQR: 6.2 – 11.9 years). Eighteen patients (90 %) were diagnosed with a DMG while two (10 %) were diagnosed with a DPHGG of the midline structures. All DMG patients harbored an H3K27 alteration, while both DPHGG patients were

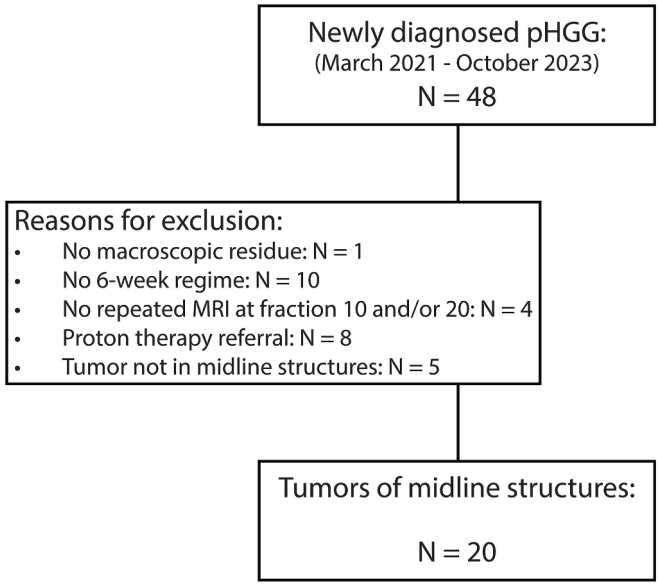

Fig. 1. Flowchart for patient selection. pHGG: pediatric-type diffuse high-grade gliomas.

Table 1
Patient, tumor and treatment characteristics.

Characteristic	N	Percentage or median (IQR)
Age (years)	20	9.1 (6.2–11.9)
Sex		
Male	10	50.0 %
Female	10	50.0 %
Interval surgery to start RT (days)	20	20 (13–23)
Interval pMRI to start RT (days)	20	13 (10–23)
Tumor histology		
DMG	18	90.0 %
H3 K27 alteration	18	100.0 %
H3.1 mutation	1	5.6 %
H3.2 mutation	2	11.1 %
H3.3 mutation	14	77.8 %
EGFR mutation	1	5.6 %
DPHGG	2	10.0 %
H3-WT/IDH-WT	2	100.0 %
Tumor location		
Pons	11	55.0 %
DMG	11	100.0 %
Non-pontine (thalamic)	9	45.0 %
DMG	7	77.8 %
DPHGG	2	22.2 %
Surgery		
Biopsy	15	75.0 %
Macroscopic subtotal resection	5	25.0 %
Radiotherapy		
54.0/1.8 Gy fractions	20	100.0 %
Concomitant treatment		
Any therapy	19	95.0 %
Temozolomide	17	89.5 %
ONC201	2	10.5 %
Corticosteroid use		
At onset of RT	9	45.0 %
At fraction 10	11	55.0 %
At fraction 20	8	40.0 %

H3- and IDH- wild type and harbored a somatic TP53 mutation. TP53 mutations were also seen in 13/18 (73 %) of the DMG subgroup. Tumors originated in the pons (11/20; 55 %) or non-pontine (thalamic area) region (9/20; 45 %). Median interval from surgery (biopsy or macroscopic subtotal resection) to start of radiotherapy was 20 days (IQR: 13 – 23 days) and median interval from pre-treatment imaging to start of radiotherapy was 13 days (IQR: 10 – 23 days). Concomitant treatment was given in 19/20 patients, in the form of temozolomide in 17/20 (85 %) and ONC201 in 2/20 (10 %).

At MRI0, the median GTV was 38.2 cm^3 (range: 17.7 – 49.4 cm^3) for pontine tumors, and 52.6 cm^3 (range: 34.9 – 195.3 cm^3) for non-pontine tumors. At rMRI10, a GTV increase of >5 % was observed in 7/20 (35 %) patients (pons: 2/11; non-pontine: 5/9). Between rMRI10 and rMRI20, in 9/20 (45 %) patients a GTV increase was observed (pons: 5/11; non-pontine: 4/9). Overall, in 12/20 (60 %) patients, a GTV increase was observed at rMR10 and/or rMR20, more specifically in 6/11 (54 %) pontine and 6/9 (67 %) non-pontine tumors (Fig. 2).

Based on dosimetric criteria for CTV and PTV, a need for plan adaptation was necessary in 3/20 (15 %) patients at fraction 10 and in 5/20 (25 %) patients at fraction 20 (Table 2). Based on the visual inspection another 12 adaptations were required. A total of 8/20 (40 %) patients required plan adaptation at fraction 10 and 12/20 (60 %) patients at fraction 20. Combining the dosimetric criteria and visual inspection, a total of 20 plan adaptations in 14 patients were required (50 % of time points required plan adaptation). In six patients the treatment plan was adapted at both rMRI10 and rMRI20. In Fig. 3, an example of the dose distribution of two patients who required plan adaptation based on violation of the dosimetric criteria (patient A) or the visual inspection (patient B) is shown.

The site of first progression was local in 19/20 patients and combined local with leptomeningeal spread in 1/20 patients. Median interval from start of radiotherapy to first progression was 8.1 months (range: 1.6–17.6 months) for the whole group, with 8.0 months for primary pons lesions (range: 2.0–17.6 months) and 8.3 months for primary non-pontine tumors (range: 1.6–15.5 months). The TTP was not significantly different between the group with versus without GTV increase during radiotherapy, respectively (median: 8.1 vs 7.6 months; $p = 0.66$) (Fig. 4).

Discussion

In this cohort of 20 pediatric patients with a newly diagnosed HGG of the midline structures undergoing a 6-week course of radiotherapy, repeated MR imaging at fraction 10 and 20 demonstrated a gross tumor volume increase of >5 % in 12/20 patients. Applying a 1.0 cm CTV expansion around the GTV resulted in a suboptimal dose coverage in 14 patients (70 %) and required adaption of their radiotherapy treatment plan. A GTV increase during radiotherapy was not associated with a shorter time to progression compared to patients who did not show an increase in GTV.

A GTV increase during radiotherapy is a well described phenomenon in adult HGG, but to the best of our knowledge has not been reported on in pediatric patients [21,22,31–33]. In two studies, large variations in tumor extent have been reported in adult patients with a glioblastoma receiving repeated MR-imaging at radiotherapy start and after every ten fractions to monitor GTV evolution [21,33]. In our evaluation, we observed a similar variation. The changeability of the GTV during radiotherapy in adults and children advocates plan adaptation. However, the relatively large margins in the range of 1.5–2.0 cm as used in the adult studies abrogates adaptation necessity. The implemented GTV-CTV margins of 1.0 cm in pediatric HGG of the midline structures might however be a potential risk for suboptimal local treatment when stationary target volumes are used [18]. Although the impact of suboptimal local treatment on time to progression of pHGG of the midline structures is difficult to assess outside the context of a randomized control trial, this cohort clearly demonstrates that using dosimetric and visual criteria, plan adaptation was needed for up to 70 % of the patients.

In pediatric patients there is limited reporting regarding offline ART. In a recent publication, a cohort of 73 pediatric patients with a mix of solid- and CNS-tumors treated with proton therapy received offline ART [34]. In this cohort, 14 % of patients required plan adaptation. However, in that cohort only three patients were treated for a HGG and did not require plan adaptation, potentially due to the larger CTV margins (up to

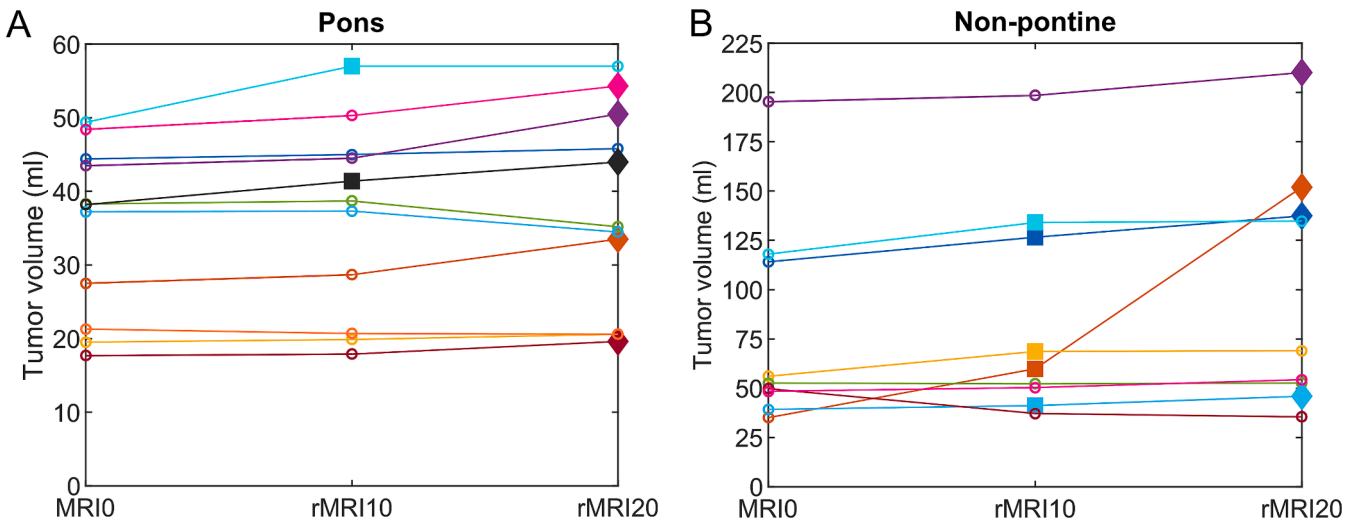

Fig. 2. Evolution of the GTV between imaging at treatment planning (MRI0) and the repeat MRIs at fraction 10 and 20 (rMRI10 and rMRI20) for patients with a tumor in the pons (A) and the non-pontine area (B). At rMRI10 and rMRI20, a square and a diamond respectively indicate a GTV volume increase >5 %.

Table 2
Total number of plan adaptations based on dosimetric criteria for CTV and PTV and visual inspection at fraction 10 and 20 (rMRI10 and rMRI20) when compared to the radiotherapy plan at MRI0. To fulfill the dosimetric criteria for CTV (D98% > 95 %) and PTV (D95% > 95 %) a minimum dose of 51.3 Gy was required. Breached dosimetric or visual criteria are highlighted in bold.

	Dosimetric criteria				**Visual**		**Total**	
	rMRI10		rMRI20		rMRI10	rMRI20	rMRI10	rMRI20
Pons	CTV D98% (Gy)	PTV D95% (Gy)	CTV D98% (Gy)	PTV D95% (Gy)				
1	51.44	51.43	51.52	51.34	0	0	0	0
2	52.25	52.15	52.01	51.73	0	**1**	0	**1**
3	52.14	52.23	52.14	52.19	0	0	0	0
4	51.86	51.65	**50.84**	**50.36**	0	**1**	0	**1**
5	51.93	51.45	51.96	51.58	0	**1**	0	**1**
6	51.84	51.89	51.82	51.88	0	0	0	0
7	52.57	52.21	52.20	**51.27**	0	**1**	0	**1**
8	52.77	52.90	52.76	52.88	**1**	0	**1**	0
9	52.16	51.98	52.07	51.76	0	**1**	0	**1**
10	53.14	53.18	53.14	53.18	0	0	0	0
11	52.87	52.90	52.74	52.66	**1**	**1**	**1**	**1**
Non-pontine								
1	51.89	51.52	**42.50**	**45.00**	**1**	**1**	**1**	**1**
2	**41.80**	**42.22**	**7.98**	**15.57**	**1**	**1**	**1**	**1**
3	**49.74**	**50.15**	52.78	52.33	**1**	0	**1**	0
4	52.40	51.84	52.36	51.73	0	**1**	0	**1**
5	53.11	53.01	53.11	53.04	0	0	0	0
6	53.26	53.01	**49.01**	**49.63**	**1**	**1**	**1**	**1**
7	51.79	51.95	51.89	52.09	0	0	0	0
8	52.35	52.16	52.31	52.21	**1**	**1**	**1**	**1**
9	**29.79**	**34.54**	52.29	52.29	**1**	**1**	**1**	**1**
Total patients	**3**		**5**		**8**	**12**	**8**	**12**

1.5 cm) and less strict dosimetric evaluation of at least >5 % decrease in V95 of the CTV required before plan adaptation. To our knowledge, no other pediatric cohorts assessing the need for ART are available in current literature, underlining the relevance of the findings in this cohort.

It is of interest to conclude that a GTV increase was not related to a significantly shorter TTP in this cohort and probably reflects a combination of patients with real progression and pseudo-progression [20]. This is best illustrated in the 4 patients with a volume increase at each repeated MRI, having a range in TTP between 1.6 and 15.4 months. In other words, GTV increase observed during this adaptive radiotherapy protocol could not be considered as a prognostic factor and a reason to switch from a 6-week normo-fractionated regimen to a hypo-fractionated regimen, or to stop radiotherapy definitely [10,12]. In addition, even though integrated pathological information was available for each patient, the rather homogeneous molecular subtyping of pHGG in this cohort did not contribute to identify patients with a shorter TTP. Lastly, plan adaptation for pHGG treated with 1.0 cm CTV margins might even delay early local progression, because of better target coverage, while potentially reducing toxicity compared to the use of larger CTV margins. However, the number of patients in this analysis is too small to support this conclusion.

This study has some limitations. Firstly, we did not acquire a repeat MRI at the start of radiotherapy. GTV increase observed at rMRI10 will have occurred in the interlude between the MRI used for planning and fraction 10 of radiotherapy. However, the intervals between surgery,

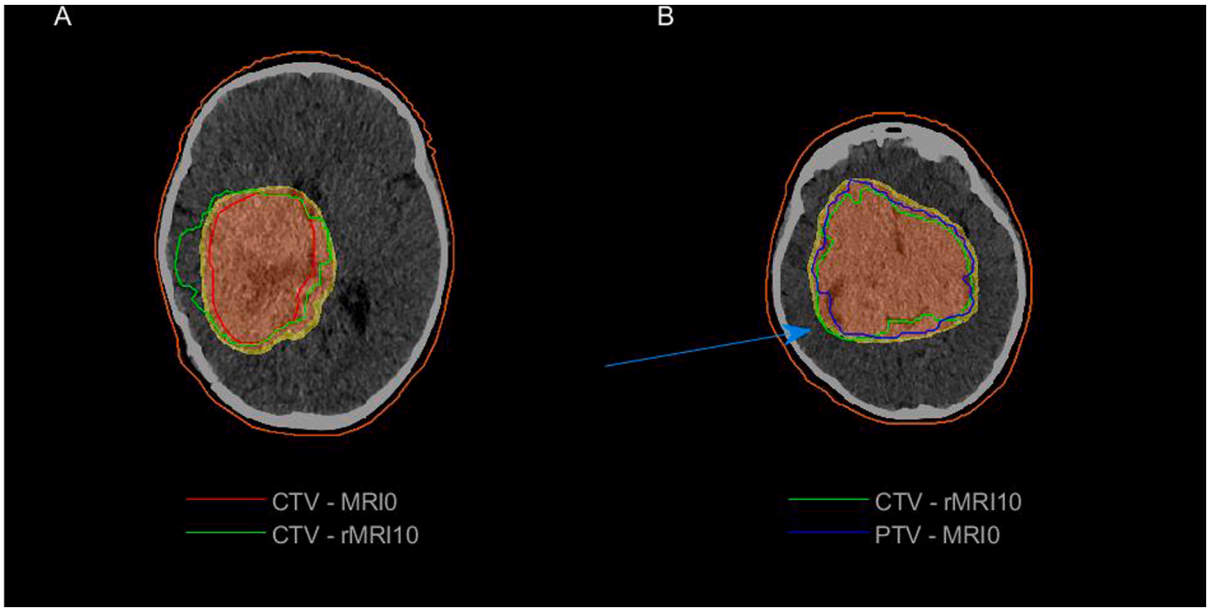

Fig. 3. Example of a patient (A) with insufficient dosimetric coverage of the CTV (D98% = 77.4 %) and PTV (D95% = 78.2 %) and a patient (B) with a dosimetrically sufficient plan (CTV D98% = 97.0 % and PTV D95% = 96.7 %), but plan adaptation was conducted based on the visual inspection of the CTV being outside of the PTV (indicated by the blue arrow). The 90 % isodose is shown in yellow and the 95 % isodose is shown in orange in both cases. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

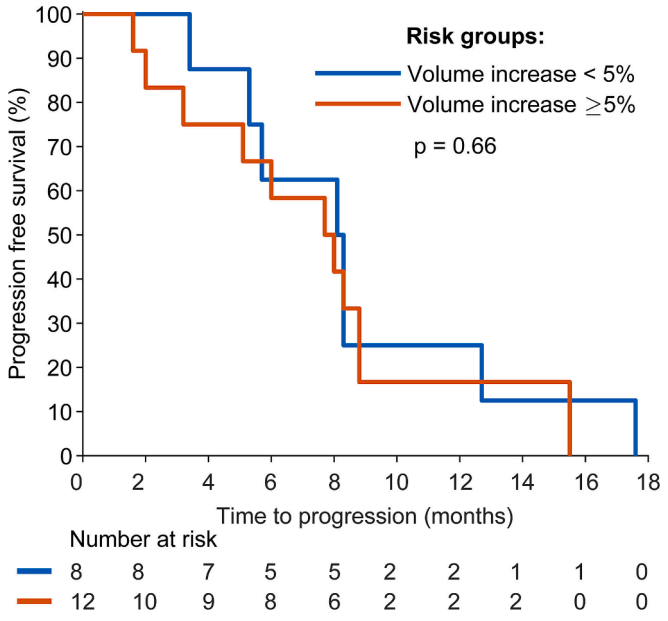

Fig. 4. Kaplan-Meier curve comparing the time to progression of patients with stable GTVs and patients with GTV increase of more than 5% at one or two time points.

pre-radiotherapy MRI and onset of radiotherapy were in accordance with daily clinical practice protocols and in case of any neurological deterioration, MRI-scans were repeated shortly before onset of radiotherapy. Secondly, offline ART is resource and time-intensive [35–37]. Whether offline ART is clinically relevant for TTP optimization compared to patients pHGGs of the midline structures treated with stationary target volumes and 1.0 cm CTV margins, cannot be inferred from this evaluation. Although the comparison might help to distinguish the effect of offline ART on TTP, we felt this was not ethical, since the use of offline ART is considered as our standard of care when using CTV expansions of 1.0 cm. If ART is not available in the clinical practice, CTV margins of 2.0 cm with anatomical boundary adaptation should be used. In our cohort, using 2.0 cm margins (and 0.2 cm PTV margin) would have resulted in only two patients who would have needed a plan adaptation at rMRI20. If per-treatment plan adaptation is not feasible, using 2.0 cm CTV margins will give adequate continued target coverage in 90 % of the patients of our cohort. This target volume increase located in the central part of the brain, however, might increase side effects and should therefore be omitted whenever feasible. Lastly, one could argue that resimulation based on clinical symptoms is sufficient. However, we think that the clinical symptoms are delayed compared to imaging changes and therefore adaptation at fixed time points is preferred. In addition, steroid use and individual patient dosage was based on clinical symptoms, but did not correlate with GTV variations. This is probably explained by the fact that steroid use in daily practice is given in different dosages across individuals and for different scenarios such as symptom reduction at presentation, edema reduction around surgery (debulking/biopsy) and/or at onset of radiotherapy.

Conclusions

In pediatric-type diffuse high-grade gliomas of the midline structures, repeated MRI during radiotherapy showed a GTV increase of >5 % in 60 % of patients. When using CTV margins of 1.0 cm, plan adaptation using offline adaptive radiotherapy is recommended to ensure persistent adequate dose coverage of the target volume. We found that a GTV increase was not correlated with a difference in time to progression, therefore we cannot recommend altering radiotherapy fractionation for a GTV increase based on this study.

Statistical analysis

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Funding statement

The authors received no financial support for the research, authorship, and/or publication of this article.

Data sharing agreement

The data used and generated in this work may be available under ethical and data protection considerations upon request to the leading institution on an individual basis.

CRediT authorship contribution statement

Fasco van Ommen: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Toon van Genechten:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis. **Mirjam E. Willemsen-Bosman:** Writing – review & editing, Methodology, Investigation, Data curation. **Max Peters:** Writing – original draft, Methodology, Formal analysis. **Enrica Seravalli:** Writing – review & editing, Supervision. **Jasper van der Lugt:** Writing – review & editing, Supervision. **Rutger A.J. Nievelstein:** Writing – review & editing, Supervision. **Sabine Mueller:** Writing – review & editing, Supervision. **Esther Hulleman:** Writing – review & editing, Supervision. **Dannis G. van Vuurden:** Writing – review & editing, Supervision. **Mariette E.G. Kranendonk:** Writing – review & editing, Supervision, Methodology. **Eelco W. Hoving:** Writing – review & editing, Supervision. **Bianca A.W. Hoeben:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Geert O. Janssens:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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