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Original Article

The impact of anatomical changes during photon or proton based radiation treatment on tumor dose in glioblastoma dose escalation trials

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ABSTRACT

Purpose/Objective: Most dose-escalation trials in glioblastoma patients integrate the escalated dose throughout the standard course by targeting a specific subvolume. We hypothesize that anatomical changes during irradiation may affect the dose coverage of this subvolume for both proton- and photon-based radiotherapy.

Material and Methods: For 24 glioblastoma patients a photon- and proton-based dose escalation treatment plan (of 75 Gy/30 fr) was simulated on the dedicated radiotherapy planning MRI obtained before treatment. The escalated dose was planned to cover the resection cavity and/or contrast enhancing lesion on the T1w post-gadolinium MRI sequence. To analyze the effect of anatomical changes during treatment, we evaluated on an additional MRI that was obtained during treatment the changes of the dose distribution on this specific high dose region.

Results: The median time between the planning MRI and additional MRI was 26 days (range 16–37 days). The median time between the planning MRI and start of radiotherapy was relatively short (7 days, range 3–11 days). In 3 patients (12.5%) changes were observed which resulted in a substantial deterioration of both the photon and proton treatment plans. All these patients underwent a subtotal resection, and a decrease in dose coverage of more than 5% and 10% was observed for the photon- and proton-based treatment plans, respectively.

Conclusion: Our study showed that only for a limited number of patients anatomical changes during photon or proton based radiotherapy resulted in a potentially clinically relevant underdosage in the subvolume. Therefore, volume changes during treatment are unlikely to be responsible for the negative outcome of dose-escalation studies.

Despite the aggressive standard treatment for patients with glioblastoma (GBM), consisting of surgery and adjuvant radio (chemo)therapy the survival of these patients remains poor [1–5]. The current radiotherapy dosing (60 Gy/30 fractions) in nonelderly glioblastoma patients is based on a historical meta-analysis by The Brain Tumor Study Group [6]. Guidelines prescribe large margins (20 mm) to include microscopic disease i.e. clinical target volume (CTV) [7,8]. Since the pattern of failure is predominantly local, this dose is probably insufficient to overcome tumor intrinsic treatment resistance. Recent efforts to increase the treatment outcome by escalating the dose report conflicting efficacy,

Abbreviations: MR_0, Radiotherapy planning MRI; MR_1, Additional MRI; T1w, T1-weighted MRI sequence; T1w_c, T1-weighted MRI sequence after administration of gadolinium contrast agent; GTR, Gross total resection; STR, Subtotal resection; SIB, simultaneous integrated boost; GTV, Gross Tumor Volume; CTV, Clinical Target Volume; PTV, Planning Target Volume; ΔCoverage, change in coverage in percentage points; $\Delta V_{<71.25Gy}$, change in CTV not receiving the minimal accepted dose of 71.25 Gy; ΔD_{min}, change in near minimum dose; $\Delta D_{95\%}$, change in dose received by 95% of the CTV volume; MGMT, O^6-methylguanine-DNA methyltransferase.

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though doses up to 75 Gy seem to be safe [9–14]. The high dose in most dose escalation trials is targeting the macroscopic tumor and/or surgical cavity as defined by MRI although ongoing trials also implement other imaging modalities [15]. The most recent and largest of dose escalation trials (NRG BN0001) randomize patients to dose escalation up to 75 Gy in 30 fractions using photon or proton based radiation treatment [16]. No improvement in overall survival was found in patients randomized to the high dose arm in the photon-based cohort [14]. The results from the proton-based dose escalation arm of this trial is awaited.

Tumor progression between surgery and the start of radiotherapy can impact clinical outcomes [17–20]. In addition, only limited data is available on anatomical changes *during* radiation treatment and it is unknown whether these may have impacted the outcome of dose escalation trials [21–25]. Yet, knowledge about such changes and their impact on the dose received by the tumor is crucial.

The purpose of our study was to determine whether clinically significant anatomical changes occurred during radiotherapy and could explain the negative outcome of dose-escalation trials targeting a sub volume of the tumor. Therefore, we are especially interested in anatomical changes during treatment and their impact on the pre-defined high radiotherapy dose areas. Photon- and proton-based dose escalated treatment plans were evaluated on a repeat MRI scan halfway the course of radio(chemo)therapy. Changes in the predefined high dose regions were analyzed to assess the impact of anatomical changes on these regions halfway the treatment.

Material and methods

Study population

Between April 2016 and January 2018, n = 24 patients with glioblastoma receiving treatment with radio(chemo)therapy underwent an additional MRI scan halfway through their treatment course (MR_1). In this study, we retrospectively evaluated the obtained MR images. This study was approved by the Medical Ethics review Committee of the Netherlands Cancer Institute (Amsterdam, The Netherlands).

All patients were diagnosed with a histologically confirmed glioblastoma multiforme (GBM, WHO Grade IV). Tumor resection was classified as Gross Total Resection (GTR) when no macroscopic tumor was visible on the T1-weighted (T1w) MR imaging sequence after administration of gadolinium contrast agent (obtained within 48 h after surgery; T1w_c). If (potential) remnant tumor was visible on the T1w_c of the postoperative MRI, this was classified as Subtotal Resection (STR) [26]. Twenty of the patients had undergone tumor resection (n = 3 GTR, n = 17 STR) and in four patients only a tumor biopsy had been taken.

The choice of the fractionation schedule was based on age and/or performance status. The applied fractionation schedules were 30 × 2 Gy (n = 19), 14 × 3 Gy (n = 3) or 15 × 2.67 Gy (n = 1). One patient received 30 × 1.8 Gy with a simultaneous integrated boost of 30 × 2 Gy. The choice of concurrent and adjuvant systemic treatment depended on age, performance status and the O^6-methylguanine-DNA methyltransferase (MGMT) methylation status. Patient and treatment characteristics are described in Table 1.

Imaging protocol

For radiation treatment planning purposes, a CT scan (CTRT, Siemens Somatom Sensation Open scanner) and a RT planning MRI (MR_0) were acquired (Philips Ingenia 3.0TMRI scanner). For the MRI examinations and CTRT, a 3-point thermoplastic head mask (Orfit Industries, Wijnegem, Belgium) was used for patient immobilization. During the course of treatment, a new MRI was acquired using the same scanning protocol (additional MRI, MR_1).

Table 1
Patient and treatment characteristics.

	Patients (n = 24)
Age at start RT (y)	60 (29–77)
Gender	
Male	14
Female	10
Surgery	
Gross total resection	3
Subtotal resection	17
Biopsy	4
MGMT status	
Methylated	4
Unmethylated	12
Unknown	8
RT schedule	
30 × 2 Gy	19
30 × 1.8 Gy + SIB 30 × 2 Gy	1
14 × 3 Gy	3
15 × 2.67 Gy	1

RT = radiotherapy; SIB = simultaneous integrated boost; MGMT = O^6-methylguanine-DNA methyltransferase.

The MRI examinations included both a T1w and T1w_c as well as a (3D) fluid-attenuated inversion recovery (FLAIR) sequence. An automated injection pump was used to inject the gadolinium-based contrast agent (Dotarem® 15 ml, Guerbet, France). The slice thickness of the T1w and T1w_c sequences were 0.9–1.2 mm and the slice thickness of the (3D) FLAIR sequence was 1.5–3 mm. The reconstructed pixel size was for the T1w and T1_c sequences 0.36 × 0.36–0.5 × 0.5 mm and for the (3D) FLAIR sequence 0.56 × 0.56–0.96 × 0.96 mm.

For the 4 patients treated with 14 or 15 fractions, the additional MR_1 was acquired after a median of 6 fractions (range 6–8 fractions), and for the remaining 20 patients this was done after 15 fractions (range 11–22 fractions).

Dose prescription and planning for in silico study

In our planning study, we followed the protocol for the experimental arm in the NRG-BN001 study for either photons or protons [27]:

(1) 50 Gy in 30 fractions to the surgical cavity, T1w_c enhanced lesions, and high FLAIR intensity region plus a margin of 2 cm (CTV_50),
(2) 75 Gy in 30 fractions (i.e. 2.5 Gy/fraction) as simultaneous integrated boost (SIB) to the T1w_c enhanced lesions and the surgical cavity plus a margin of 5 mm (CTV_75).

The CTV_50 and CTV_75 were delineated on the MR_0 and the MR_1. Both the CTV_50 and CTV_75 were expanded with 4 mm to obtain the Planning Target Volume (i.e. PTV_50 and PTV_75, respectively; Fig. 1). To minimize the uncertainties in target volume delineation, the delineations were made by one author and reviewed by an independent observer (neuro-oncology dedicated radiologist who was blinded for the MR_0 and MR_1 information). The pre- and postoperative MR images were available for tumor and surgical cavity evaluation. The organs at risk (OAR's) were delineated according to the NRG-BN001 protocol [27].

All patients were planned according to both the protons and photons planning protocols as if they had been treated in the experimental arm of the study. The complete planning protocol

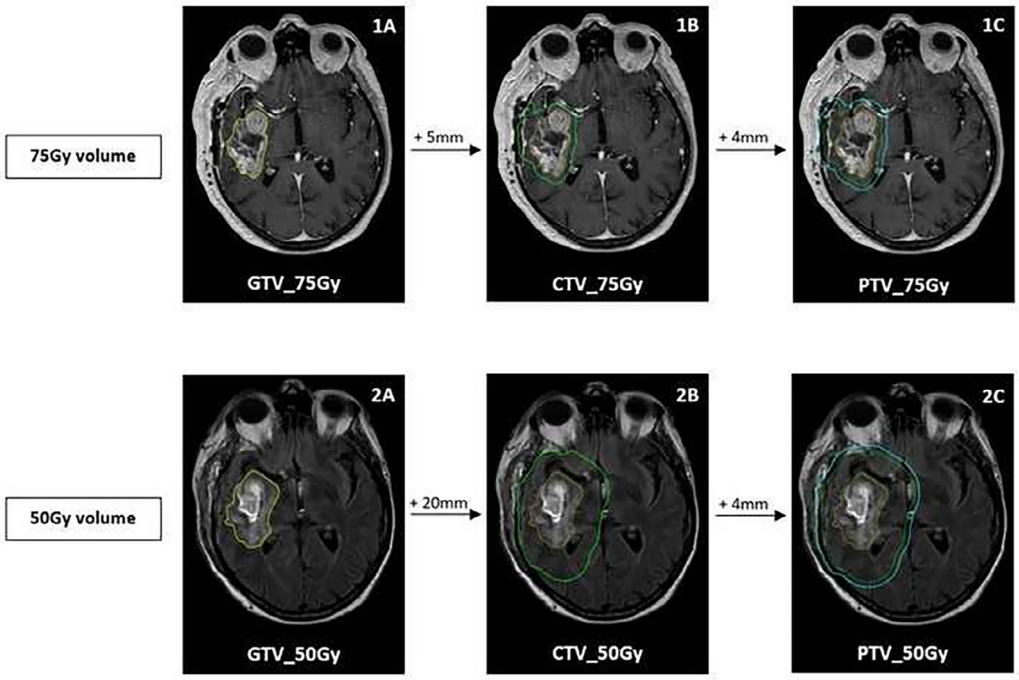

Fig. 1. Example of boost volumes (1A–1C) and target volumes (2A–2C). MRI 1A–1C: Contrast enhanced T1 sequence; MRI 2A–2C: Fluid-attenuated inversion recovery sequence. GTV = Gross Tumor Volume; CTV = Clinical Target Volume; PTV = Planning Target Volume.

is described in the NRG-BN001 protocol [27]. In summary, ≥95% of the target volume (PTV for photons and CTV for protons) is to receive a dose of 50 Gy (minimum ≥47.5 Gy for the PTV_50 or CTV_50, respectively) and of 75 Gy to the PTV_75 or CTV_75 (with ranges of 71.25–78.75 Gy as acceptable variations). In this study, the radiation dose (Gy) for protons was corrected for its relative biological effectiveness (RBE) using a factor of 1.1 [28].

The photon plans were created with Pinnacle v. 9.10 (Philips Radiation Oncology Systems, Fitchburg, WI) and volumetric modulated arc therapy (VMAT) was used. The treatment was planned to the PTV_50 and 75 with non-coplanar arc technique.

Proton treatment plans were calculated using RayStation (Research v 5.99, RaySearch Laboratories AB, Stockholm, Sweden) and intensity modulated proton therapy (IMPT) with pencil beam scanning (PBS) for beam delivery. Treatment plans were created for each patient using a robustly optimized plan with four radiation beams (2 for CTV_50 and 2 for CTV_75, respectively). The robust plans were generated optimizing the target coverage for the CTV as done in clinical practice, thus no PTV concept was used. For details see the supplementary methods in the appendix.

The dose limits to the OARs were not exceeded (Table S1). The dosimetric differences in the OARs between the photon and proton treatment plans were not subject of our study.

Data evaluation

The CTV margin is applied to account for microscopic disease beyond the contrast enhanced lesion and is independent of the used treatment modality. In contrast, for physics related uncertainties, different principles of margins are used in photon- and proton-based treatment. In this study we focused on the dose delivered to the CTV to evaluate similar dose parameters.

To determine the impact of the target volume changes on target coverage, the dose distribution of the original treatment plan (based on MR_0) was propagated to MR_1 for both the simulated photon and proton treatment plans (Fig. 2). We only analyzed the effects of anatomical changes on the CTV_75 since the effect of anatomical changes on the high experimental dose regions is of particular interest. We calculated the;

1) $\Delta Coverage$ = change in percentage (i.e. crude % change) of the CTV_75 volume receiving the minimal accepted dose (i.e. 71.25 Gy),
2) $\Delta V < 71.25\ Gy$ = change in CTV_75 volume that did not receive the minimally accepted dose,
3) ΔD_{min} = change in D98%, which is the near minimal dose
4) ΔD95% = change in minimum coverage dose of 95% of the CTV_75 volume (this parameter was used as constraint in the NRG-BN001 protocol [27]).

All analyses were performed using IBM SPSS Statistics software version 22 (IBM corp., Armonk, NY).

Results

The median time between MR_0 and MR_1 was for the twenty patients having thirty fractions 27 days (range 20–37) and for the four patients having fourteen or fifteen fractions 17 days (range 16–19). In this time the median volume of CTV_75 decreased with 0.5 cc (range −38.3 to +39.6) and increased with 12.9 cc (range −4.4 to +19.7), respectively. There was no significant correlation between the MR_0–MR_1 interval and the change in CTV_75 volume (long course Spearman's rho $r = 0.040$ ($p = 0.866$) and short course $r = 0.316$ ($p = 0.684$)). For the whole group, the median time between surgery and start of radiotherapy, and MR_0 and start of radiotherapy was 33 days (range 24–50 days) and 7 days (range 3–11 days), respectively. Sixteen patients received dexamethasone during radiation treatment.

Most patients showed only a minimal change of the dose parameters half-way the treatment (Fig. 3, Table 2). Three patients (12.5%) experienced an obvious deterioration of the treatment plan

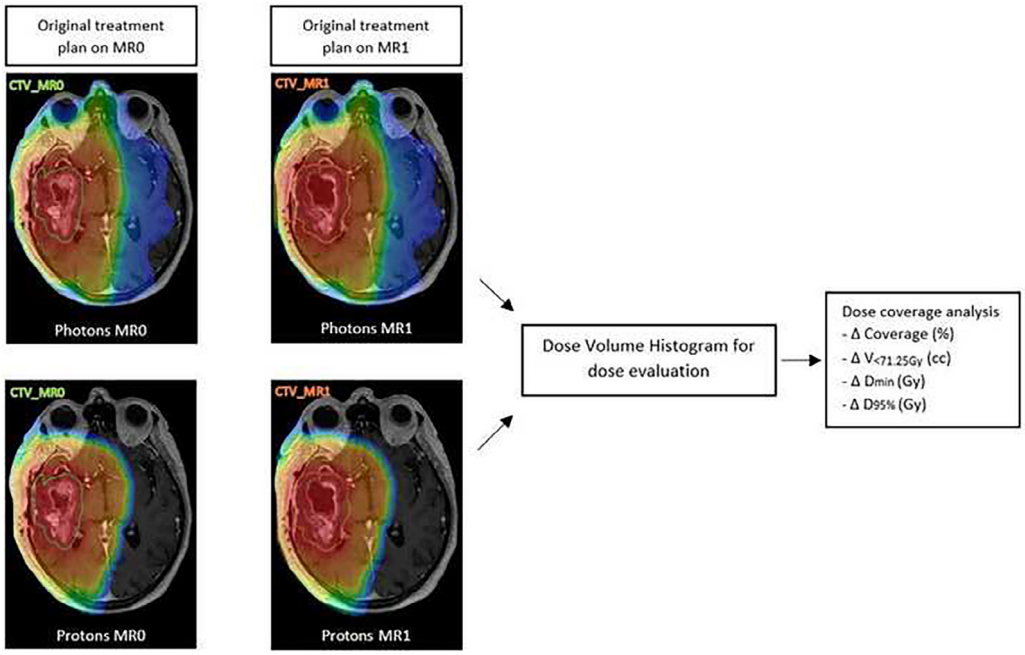

Fig. 2. Overview material and methods. For photons the treatment plan was simulated on the PTV of MR_0. For protons the treatment plan was simulated on the delineated CTV of MR_0. The dose volume histogram is used to evaluate the dose distribution on the CTV based on MR_1. MR_0 = Radiotherapy planning MRI; MR_1 = Additional MRI; CTV = Clinical Target Volume; PTV = Planning Target Volume; ΔCoverage = change in coverage in percentage points; $\Delta V_{<71.25Gy}$ = change in CTV not receiving 71.25 Gy; ΔD_{min} = change in near minimum dose; $\Delta D_{95\%}$= change in dose received by 95% of the CTV.

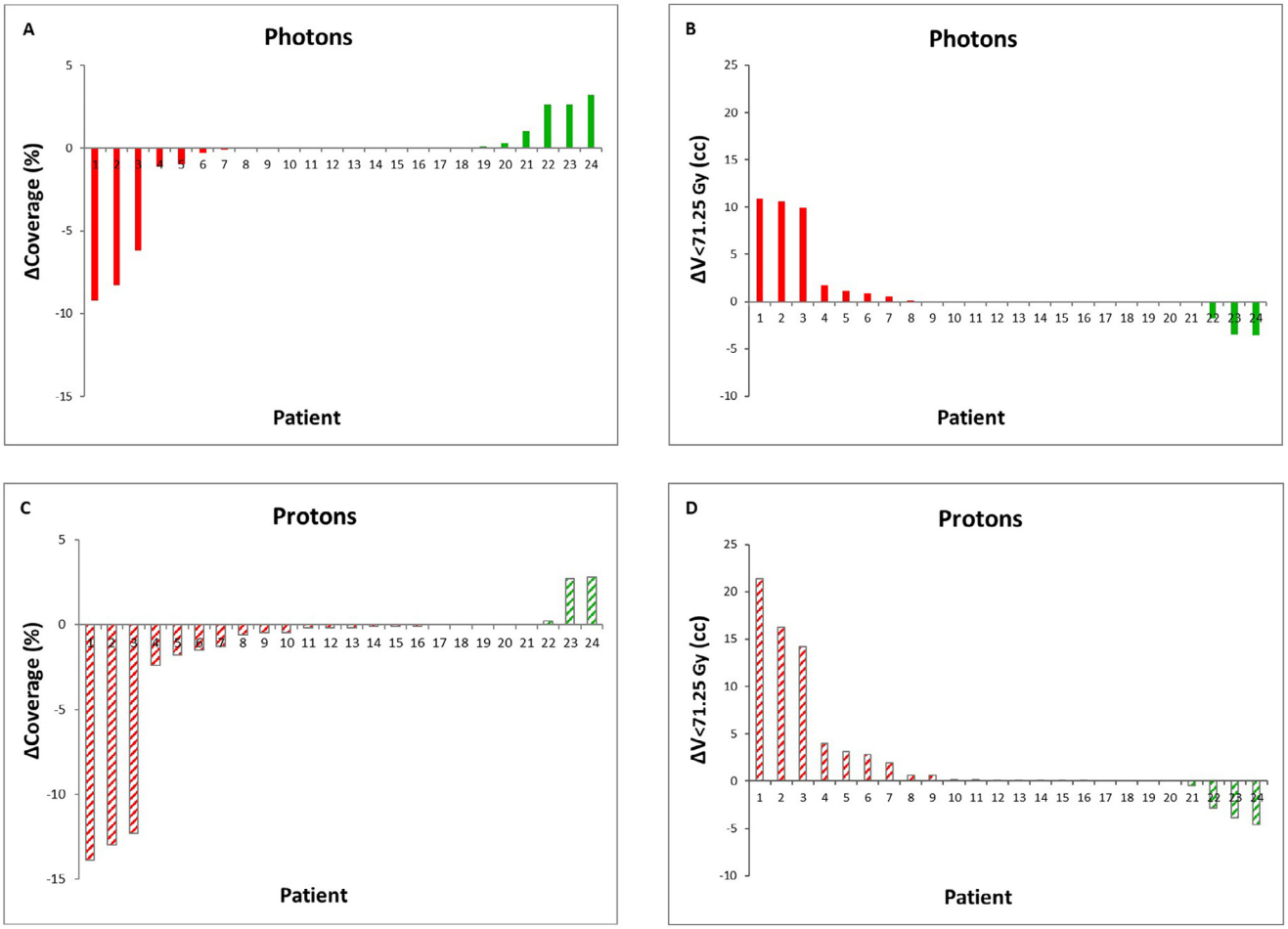

Fig. 3. Change in CTV coverage with 71.25 Gy (crude change in percentage points; A + C) and $V_{<71.25Gy}$ (volume of CTV receiving <71.25 Gy; B + D) between MR_1 and MR_0. MR_0 = Radiotherapy planning MRI; MR_1 = Additional MRI; CTV = Clinical Target Volume.

(Fig. 3A). For these patients, the ΔCoverage decreased with ≥5% and at least 10 cc did not receive the required minimum dose of 71.25 Gy ($V_{<71.25Gy}$, Fig. 3B) during treatment. These three patients all had a sub total resection and underwent a long course of radiotherapy. The $D_{95\%}$ decreased between 3.2 and 11.7 Gy (supplementary fig. S2) and two of these patients also experienced a severe worsening of the D_{min} (12.6 and 16.4 Gy, Fig. 4) whereby the D_{min} of the third patients was already impaired (54.9 Gy) due to the close proximity to the brain stem and therefore changed minimally (1.4 Gy increase). In two patients the cystic component of the tumor increased significantly which explains the large change in dose parameters. In the third patient the contrast enhanced lesion increased.

For another three patients (12.5%), the dose coverage improved over the course of treatment (Fig. 3A + B). All these three patients received a long course of radiotherapy. Two of these patients underwent a STR and the other patient a biopsy. The two patients who underwent a STR showed a decrease of both the surgical cavity and the hematoma on MR_1. One patient also showed a decrease in the contrast enhancing volume. There was no difference between the short and long course group for the any of the dose parameters.

Considering the Planning Target Volume (i.e. PTV_75, which takes different physics related uncertainties into account like patient position variability), seven patients (29%) experienced an obvious deterioration of the treatment plan (Supplementary Fig. S1).

For the proton treatment plans we found similar results compared to the photons. The three patients showing a worsening of the ΔCoverage of the CTV_75 for the photon plan had similarly worse ΔCoverage in the proton plans (of more than 10%; Fig. 3C). For these patients, the $V_{<71.25Gy}$ was up to 21.37 cc (Fig. 3D, Table 2), the D_{min} decreased with 2.4–15.7 Gy and the $D_{95\%}$ with 4.2–10.8 Gy (Fig. 4 and Supplementary Fig. S2 respectively). Two of the three patients that showed improved parameters according to the photon plan also had improvement according to the proton treatment plans (Fig. 3).

Discussion

This study assessed the dosimetric effects caused by anatomical changes during radiotherapy for both photon- and proton-based dose-escalated radiation treatment in patients with glioblastoma. Overall the changes were minimal but in a subset of patients (12.5%) we found a serious deterioration of the dose coverage on the additional MRI during radiotherapy.

Bernchou et al. analysed the GTV coverage for 29 glioblastoma patients during standard treatment (59.4 Gy/33fractions to whole target volume) at fraction 10 and 20. In this study a

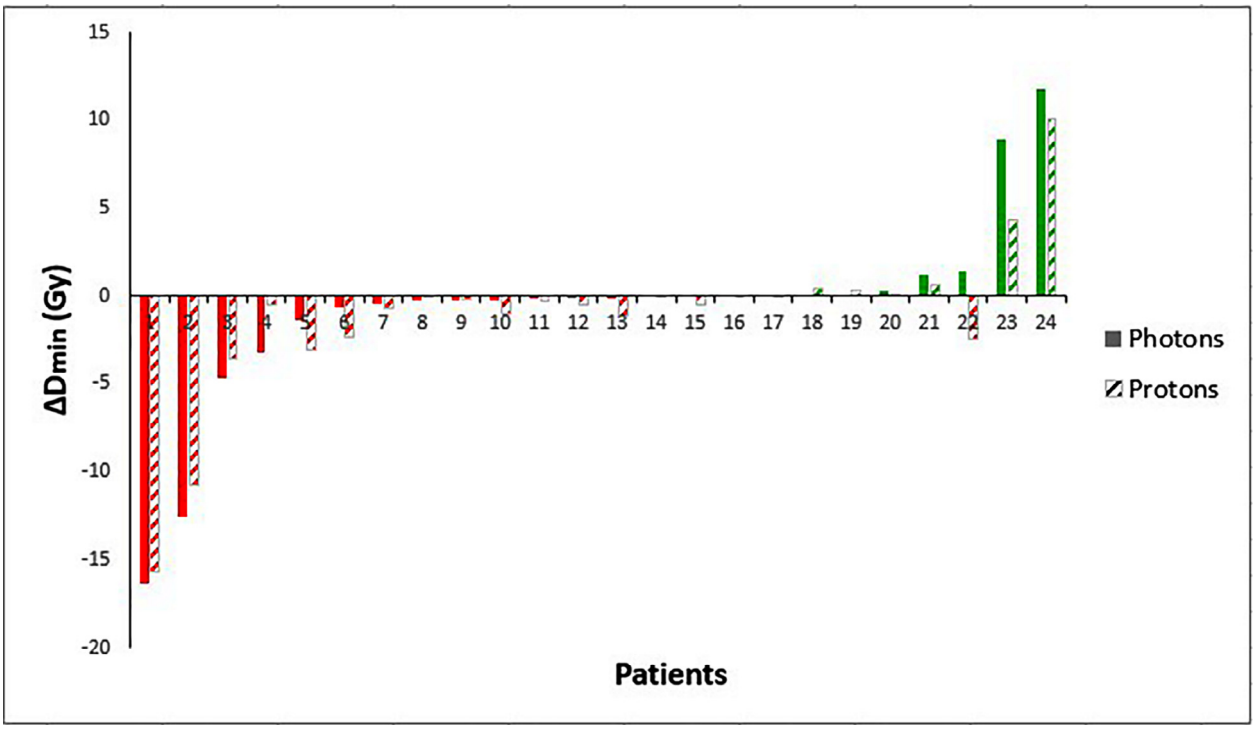

Fig. 4. Change in minimum dose D_{min} (Gy) between MR_1 and MR_0. Red indicates a decrease and green an increase in D_{min}. MR_0 = Radiotherapy planning MRI; MR_1 =- Additional MRI.

Table 2
Median change between MR_1 and MR_0 for the different dose parameters.

	ΔCoverage (%)	$\Delta V_{<71.25Gy}$ (cm^3)	ΔD_{min}(Gy)	$\Delta D_{95\%}$ (Gy)
CTV Photons (n = 24)	0 (range −9.2 to +3.2)	0 (range −3.53 to +10.93)	−0.1 (range −16.4 to +11.8)	−0.1 (range −11.7 to +3.9)
CTV Protons (n = 24)	−0.2 (range −13.9 to +2.8)	0.1 (range −4.57 to +21.37)	−0.4 (range −15.7 to +10.1)	−0.1 (range −10.8 to +3.2)

MR_0 = Radiotherapy planning MRI; MR_1 = Additional MRI; CTV = Clinical Target Volume; ΔCoverage = change in coverage in percentage points; $\Delta V_{<71.25Gy}$ = change in CTV not receiving 71.25 Gy; ΔD_{min} = change in near minimum dose; $\Delta D_{95\%}$ = change in dose received by 95% of the CTV.

10–20 mm CTV, and 3 mm PTV margin was used to expand the GTV (defined as the surgical cavity and contrast-enhancing tumor). The GTV coverage during treatment was >99.6% and no adaptation of the initial plan was recommended for any of the patients [24]. In our study we used the smaller dose-escalation defined margins (CTV 5 mm, PTV 4 mm) and planning dose constraints of the most recent and largest dose-escalation trial [16] and found for a small subset of patients that the dose halfway the treatment would not meet the dose constraints of the original plan. Future studies using smaller margins should consider the potential of volume changes and inclusion of repeat imaging during treatment.

There can indeed be an impact of anatomical changes on the outcome of dose-escalation trials, but it is unlikely to explain the negative results of dose-escalation trials to its full extend. The lack of repetitive longitudinal imaging in clinical dose-escalation studies (e.g. detailed information on functional and anatomical changes before, during and after the treatment) hampers the understanding why dose-escalation have been negative so far. It remains therefore unclear whether it is the intrinsic radio resistance, the wrongly targeted area or timing (or a combination) that is underlying the negative results.

Dose escalation in trials, are targeting a sub volume of the tumor defined as the contrast enhancing area on the T1-weighted MRI and the surgical cavity. This target volume is preferably contoured on a dedicated RT planning MRI scan, although some institutes still use the postoperative MRI. In this study there was a relatively short interval between the dedicated RT planning MRI and the initiation of treatment (median 7 days). One can expect larger variations in dose parameters during treatment if no dedicated RT MRI scan is acquired (due to tumor progression and changes in surgical cavities) [18,20,29]. Another limitation of our study is the inclusion of four patients with a shortened treatment regimen. These two factors may have resulted in an underrepresentation of the percentage of patients with severe anatomical changes with longer intervals.

Anatomical changes can also have an impact on the dose to normal brain tissue and organs at risk. Multiple studies showed a benefit for proton beam therapy limiting the dose to OARs although the clinical benefit is still under debate [30–33]. In our study we strictly followed the constraints for the OARs in the planning protocol. The dose to the target volume was adjusted to meet these constraints, whereas in a clinical setting it may be considered otherwise. A subset of patients in our study experienced a decrease of the area receiving a higher dose, whereby an adjusted treatment plan half-way the treatment could potentially lower doses to normal tissues.

Due to the improved quality of (in-)treatment imaging and delivery techniques the physics related uncertainty margins are decreasing over time whereas the biology related margins taking the microscopic disease into account remain large and uncertain [8,34]. The concepts of margins between proton and photon treatment are different and often the topic of discussion in studies comparing treatment plans. For photon treatments the concept of a concentric uncertainty margin is still widely accepted. However, for proton planning individual (beam dependent) uncertainties are being used. Due to these differences, we evaluated the dose delivered to the biology defined CTV margin.

This study showed that for a subset of patients who underwent a subtotal resection, the received dose may differ substantially from the planned dose half-way the treatment for both photons and protons in a dose escalation setting due to anatomical changes. Since this is only in a small number of patients, we conclude that the volume changes during treatment are not likely to be the reason for the negative outcome for dose-escalation trials. Nevertheless, trials that aim to improve the treatment outcome by using dose escalation or dose-painting need to consider implementation of repetitive longitudinal imaging to contribute to a better understanding of the poor outcome of glioblastoma patients and how to develop better treatment strategies.

Disclosure

E. Hessen receives financial support from the Antoni van Leeuwenhoek foundation. The study received no industry funding. There is no conflict of interest for any of the authors.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.09.022.

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