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Original Article

Evolution of the gross tumour volume extent during radiotherapy for glioblastomas

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ABSTRACT

Background and purpose: Tumour growth during radiotherapy may lead to geographical misses of the target volume. This study investigates the evolution of the tumour extent and evaluates the need for plan adaptation to ensure dose coverage of the target in glioblastoma patients.
Materials and methods: The prospective study included 29 patients referred for 59.4 Gy in 33 fractions. Magnetic resonance imaging (MRI) was performed at the time of treatment planning, at fraction 10, 20, 30, and three weeks after the end of radiotherapy. The gross tumour volume (GTV) was defined as the T1w contrast-enhanced region plus the surgical cavity on each MRI set. The relative GTV volume and the maximum distance (D_{max}) of the extent of the actual GTV outside the original GTV were measured. Based on the location of the actual GTV during radiotherapy and the original planned dose, a prospective clinical decision was made whether to adapt the treatment.
Results: Dose coverage of the GTV during radiotherapy was not compromised, and none of the radiotherapy plans was adapted. The median D_{max} (range) was 5.7 (2.0–18.9) mm, 8.0 (2.0–27.4) mm, 8.0 (1.9–27.3) mm, and 8.9 (1.9–34.4) mm at fraction 10, 20, 30, and follow-up. The relative GTV volume and D_{max} observed at fraction 10 were correlated with the values observed at follow-up (R = 0.74, $p < 0.001$ and R = 0.79, $p < 0.001$, respectively).
Conclusion: Large variations in the GTV extent were observed, and changes often occurred early in the treatment. Plan adaptation for geographical misses was not performed in our cohort due to sufficient CTV margins.

 Radiotherapy and Oncology 160 (2021) 40–46

Despite aggressive treatment consisting of maximal surgical debulking followed by radiotherapy (RT), and concomitant and adjuvant temozolomide (TMZ) [1], the prognosis for glioblastoma multiforme (GBM) patients remains poor with 2 years survival rate around 26% [2,3]. Since the late 1970s, RT has been part of standard treatment for patients with GBMs. Initially, whole-brain irradiation was applied, but the morbidity related to this treatment and the documentation of treatment failures primarily being local recurrences introduced regional radiation fields [4]. Furthermore, the introduction of computed tomography (CT) and magnetic resonance imaging (MRI) initiated the era of conformal RT during the last decades. However, RT is still delivered to large volumes including the gross tumour with an extensive margin.

The definition of RT target volumes varies among different institutions [5]. Danish patients are treated according to the European Association for Neuro-Oncology (EANO), which defines the gross tumour volume (GTV) as the residual enhancement on T1w MRI plus the surgical cavity. In the EANO guidline a 1.5–2.5 cm margin, including the post-operative peritumoral oedema (hyperintense region on T2w MRI), is suggested to define the clinical target volume (CTV) [6].

Abbreviations: CT, Computed tomography; CTV, Clinical target volume; D_{max}, Maximum distance; EANO, European Association for Neuro-Oncology; ECOG, Eastern Cooperative Oncology Group; FLAIR, Fluid-attenuated inversion recovery; GBM, Glioblastoma multiforme; GTV, Gross tumour volume; GTV_{10}, GTV delineated on MR_{10}; GTV_{20}, GTV delineated on MR_{20}; GTV_{30}, GTV delineated on MR_{30}; GTV_{FU}, GTV delineated on MR_{FU}; GTV_P, GTV delineated on MR_P; MRI, Magnetic resonance imaging; MR_{10}, MRI acquired at fraction 10; MR_{20}, MRI acquired at fraction 20; MR_{30}, MRI acquired at fraction 30; MR_{FU}, MRI acquired at follow-up; MR_P, MRI acquired for treatment planning; R-GTV, The relative GTV volume; RT, Radiotherapy; RTOG, Radiation Therapy Oncology Group; TMZ, Temozolomide.

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RT is typically delivered over 6–7 weeks, and from the clinical setting, it is well known that some GBM patients may deteriorate during this period, to a degree that precludes completion of the treatment. These patients often have large tumour growth during RT as verified by ad hoc MRI. Previous studies have shown that tumour volume changes often occur between the post-operative MRI and the planning MRI [7,8], but only a few studies have evaluated the changes in tumour volume during RT [9–15]. In the largest study published so far, Leitzen et al [10] reported that 36% of 64 GBM patients had an MRI verified increase in the tumour size observed halfway through treatment.

For patients with large tumour growth during RT, there is a risk of a geographical miss if the tumour extends outside the planned volume of radiation. Such patients might benefit from adapting the treatment according to the target extent during the treatment course. However, it is currently unknown how many patients this applies to, and when to perform additional MRI for plan adaptation. Furthermore, it is not known how the tumour extent evolves or whether early changes are related to changes observed later during treatment or at follow-up. Such information might be useful for early stratification of patients into groups with modified therapy or supportive care. The current study investigated the evolution of the tumour extent during RT and prospectively evaluated the clinical decision to perform RT plan adaptions during the treatment to achieve target coverage for glioblastoma patients included in a prospective trial in which MR imaging was performed at multiple time points after RT planning.

Methods

Patients

A total of 29 patients with newly diagnosed histologically verified GBM (WHO grade 4) allocated to RT (59.4 Gy in 33 fractions) were prospectively included in the study from February 2018 to May 2019. Inclusion criteria were age $\geq$18 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, clinically fit for long-term radiotherapy and concomitant and adjuvant TMZ, and no contraindications for MRI or contrast agent. All patients received verbal and written information and signed informed consent before treatment. The project was approved by the Scientific Ethical Committee of the Region of Southern Denmark (project identification number: S-20170128) and the Data Protection Agency. Patient characteristics are shown in Table 1.

Table 1
Patient characteristics.

Characteristic	Number of patients (%) unless otherwise indicated
Age (median, range) [years]	66 (35–75)
Gender	
Female	12 (41%)
Male	17 (59%)
Initial symptoms*	
Headache	6 (21%)
Seizure	8 (28%)
Focal deficit	21 (72%)
Cognitive	7 (24%)
Location	
Frontal	12 (41%)
Parietal	8 (28%)
Occipital	4 (14%)
Temporal	5 (17%)
Surgery	
Biopsy	7 (24%)
Partial resection	9 (31%)
Total resection	13 (45%)
Histology	
Glioblastoma (WHO grade IV)	29 (100%)
MGMT status	
Unmethylated	13 (45%)
Methylated	13 (45%)
Unknown	3 (10%)
ECOG performance status	
0	15 (52%)
1	9 (31%)
2	5 (17%)
Steroids before RT	
Yes	20 (69%)
No	9 (31%)

Abbreviations: MGMT = O(6)-Methylguanine-DNA methyltransferase, ECOG = Eastern Cooperative Oncology Group.
* 62% monosymptomatic, 38% more than one symptom.

Image acquisition

The patients were immobilised in Orfit three-point reinforced Efficast masks (Orfit Industries NV, Belgium) fixed to a base plate. Treatment planning CT scans using intravenous Omnipaque contrast agent (GE Healthcare, United States) were acquired on either a Toshiba Aquillion One (Canon Medical Systems Corporation, Japan) scanner (n = 22) using a slice thickness of 1 mm or a Philips Big Bore Brilliance (Philips Medical Systems BV, The Netherlands) scanner (n = 7) using a slice thickness of 1.5 mm. In all cases, an in-plane pixel size of 1 $\times$ 1 mm^2 and a 512x512 matrix was used.

MRI scans were acquired with patients immobilised in the treatment position on a Philips Ingenia 1.5 T (Philips Medical Systems BV, The Netherlands) system equipped with a flat tabletop and using two Flex L coils. T1w 3D fast field echo scans (TE = 3.8 ms, TR = 25 ms, FA = 30°) were acquired both with and without intravenous gadolinium contrast (Gadovist, Bayer HealthCare, United Kingdom) using a reconstructed slice thickness of 1 mm, an in-plane pixel size of 1 $\times$ 1 mm^2, and a 232 $\times$ 232 matrix. T2w 3D fluid-attenuated inversion recovery (FLAIR) scans (TE = 294 ms, TR = 4800 ms, TI = 1660 ms) were acquired with a slice thickness of 3 mm, an in-plane pixel size of 0.7 $\times$ 0.7 mm^2, and a 192 $\times$ 189 matrix. Besides acquiring these MRI scans as part of the RT treatment planning (MR_P), image sets were also acquired on treatment fraction 10, 20, and 30 (MR_{10}, MR_{20}, MR_{30} – allowing a variation of +/− two days), and also at follow-up three weeks after the end of RT (MR_{FU}). MRI scans acquired during the treatment course were performed after delivery of the daily RT fraction. All MRI scans were acquired at the same MRI system dedicated for RT planning.

Radiotherapy planning

The patients were treated according to the Danish Neuro-Oncology Group guidelines [16]. MR_P scans were imported into the treatment planning system Pinnacle (Philips Healthcare, The Netherlands) version 14.0 or 16.0 and co-registered with the CT scan used for RT treatment planning. The treatment planning GTV (GTV_P) was outlined in collaboration between a radiation oncologist and a radiologist as the surgical cavity and any remaining contrast-enhanced tumour defined on T1w images. For 26 patients the CTV was subsequently constructed using a 20 mm isotropic expansion of the GTV_P, excluding anatomical barrier structures (bone, cerebellar tentorium, and falx cerebri) and critical organs at risk (optic nerves, chiasm, and brain stem) unless direct tumour involvement. In three cases the CTV margin was reduced to 15 mm (n = 1) or 10 mm (n = 2) due to large GTVs, and in some cases (n = 6), the CTV was slightly extended to cover part of the

hyperintense area on the T2/FLAIR scan outside the isotropic expansion at the clinician's discretion. The planning target volume (PTV) was created from the CTV by the addition of a 3 mm margin.

The patients were prescribed 59.4 Gy in 33 fractions. The dose was prescribed according to the International Commission on Radiation Units recommendation [17]. At least 95% of the prescribed dose should cover at least 98% of the PTV. Target coverage was potentially limited by the proximity of critical organs at risk. Treatment was delivered as one arc VMAT on Elekta Versa HD accelerators (Elekta Instrument AB, Sweden) using daily cone-beam CT image-guidance and 6D couch corrections to reduce translational and rotational setup errors [18].

Plan adaptation

During the RT treatment course, MR_{10} and MR_{20} scans were imported in Pinnacle and co-registered with the planning scans. Based on the location of the current T1w contrast-enhancing region plus the surgical cavity with respect to the original planned dose, an evaluation of geographical misses was performed, and a clinical decision was made by the treating radiation oncologist whether to continue with the original RT treatment plan or to adapt the treatment based on the present suspected tumour extent.

GTV structure comparison

MRI scans acquired at fraction 30 and follow-up were not used to evaluate the need for plan adaptation, but as part of the current study, MR_{30} and MR_{FU} were also imported in Pinnacle and co-registered with the planning scans. The GTV was re-delineated on MR_{10}, MR_{20}, MR_{30}, and MR_{FU} using a similar approach as for MR_P. This resulted in five GTV delineations (GTV_P, GTV_{10}, GTV_{20}, GTV_{30}, and GTV_{FU}) for each patient. All re-delineations were performed by the same radiation oncologist in consensus with a neuroradiologist.

All structure sets were exported from Pinnacle to Matlab (The MathWorks Inc, United States) for further analysis. The relative GTV volume (R-GTV) was defined by the ratio of actual and the original GTV volume as an estimate of changes of the tumour burden during RT. Furthermore, the maximum extension distance (D_{max}) from any point on the GTV_X contour outside of GTV_P to the closest point on the GTV_P was measured. Thus, D_{max} measures how far a GTV_X maximally extend from the surface of GTP_P.

Statistical analysis

Population changes throughout the treatment course and at follow-up were tested by Wilcoxon signed-rank tests. Associations between variables were analysed by Spearman's rank correlation coefficient. Statistical significance was at the 5% level.

Results

All patients completed RT. All except one patient completed the schedule of concomitant TMZ. The majority of the patients (n = 24) received adjuvant TMZ, 14 patients completed all six series. All except for three MRI sets were acquired according to the protocol: For one patient the MR_{30} scan session was not booked correctly, another patient did not show up for the MR_{FU} scan, while for a third patient the MR_{30} scan was stopped prematurely due to patient movement. The median time (range) from surgery to MR_P and MR_P to initiation of RT was 27 (17–36) days and 7 (6–11) days, respectively. The median time (range) from MR_P to MR_{10}, from MR_{10} to MR_{20}, from MR_{20} to MR_{30}, and from MR_{30} to MR_{FU} was 21 (15–30) days, 14 (11–21) days, 14 (10–21) days, and 26 (18–38) days, respectively. The volume of GTV_P is shown for each patient in supplementary Fig. 1, where the patients are numbered according to the rank of the GTV_P volume.

The prospective clinical evaluation of the extent of the T1w contrast-enhancing region plus surgical cavity with respect to the original planned dose at fraction 10 and 20 did not lead to adaptation of the RT plan during the treatment course for any of the included patients. The percentage volume of the original CTV and the percentage volume of the GTV at fraction 10, 20, and 30 covered by 95% of the prescribed dose is shown in Fig. 1A. Two patients had GTV coverage below 100% during RT, however, the minimum coverage was 99.7% which was sufficient to continue RT without plan adaptation based on the ICRU dose coverage recommendations. This is also confirmed by the minimum dose ($D_{98\%}$) to the GTV at planning and at fraction 10, 20, and 30. In no cases did $D_{98\%}$ fall below 95% (Fig. 1B). In Fig. 2 selected slices from MR scans acquired prior, during, and after RT is shown for four cases.

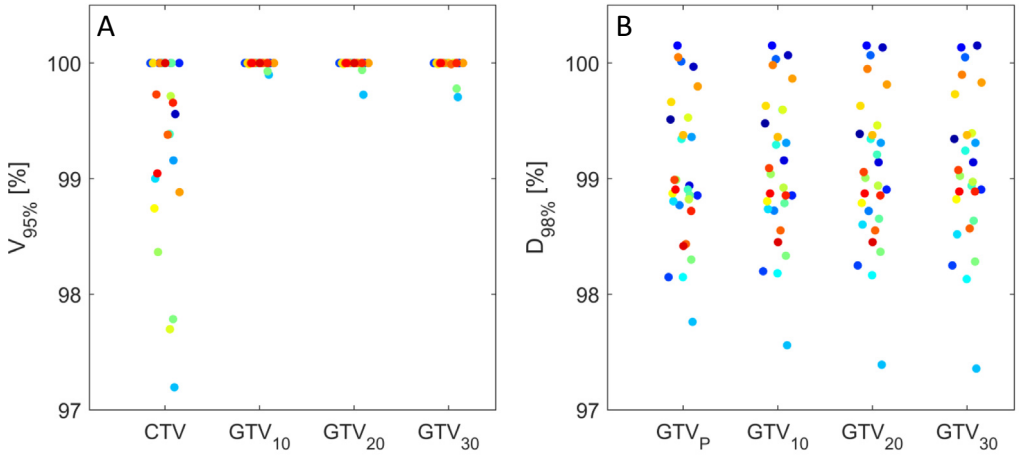

Fig. 1. (A) The percentage volume of the original CTV as well as the GTV at fraction 10, 20, and 30 covered by 95% of the prescribed dose. Dose coverage of the CTV was less than 99% in six patients due to close proximity of normal tissue – primarily the brain stem. (B) The minimum dose that covers 98% of the GTV at planning and at fraction 10, 20, and 30. The colour code in both plots is from supplementary Fig. 1.

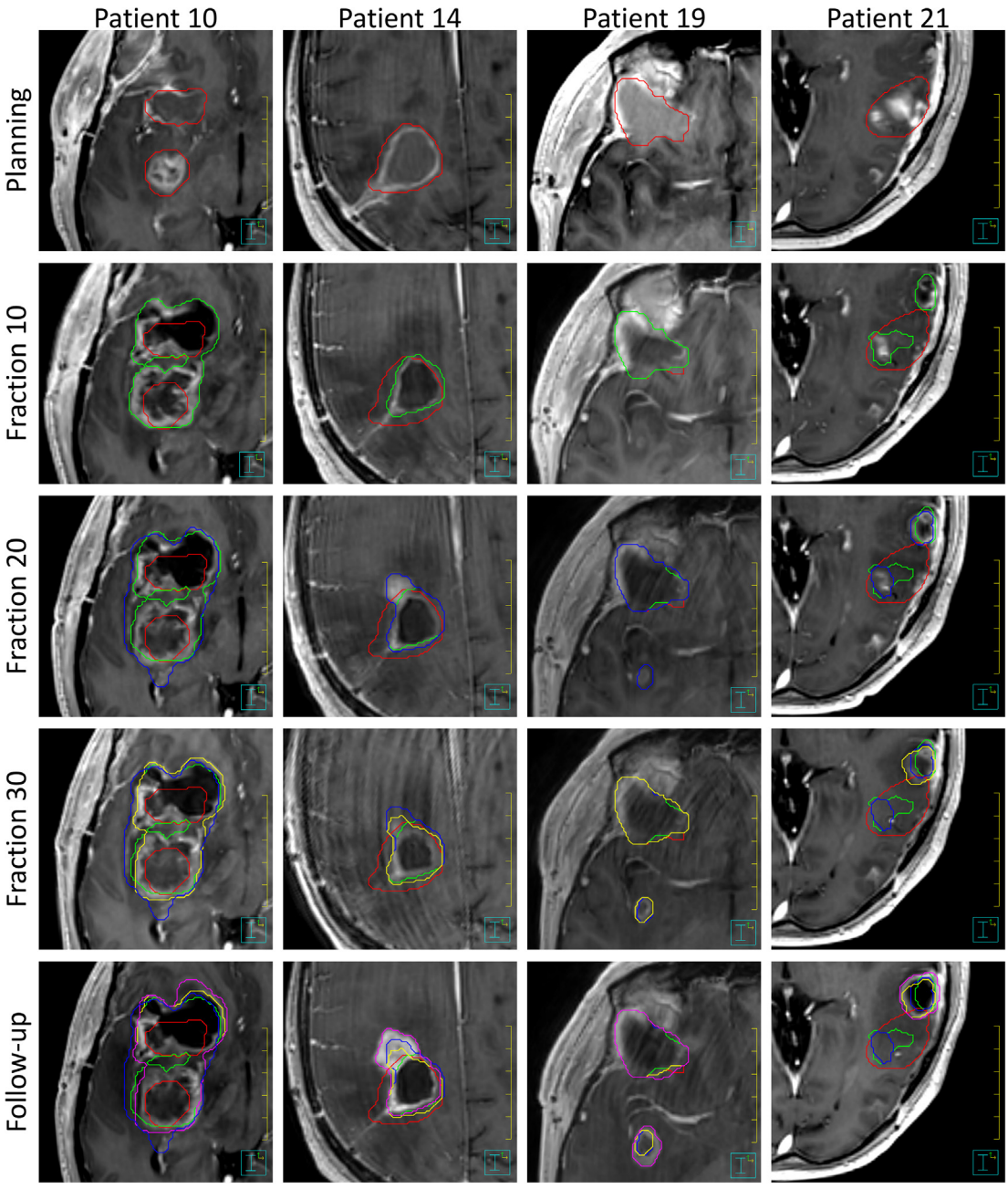

Fig. 2. Selected slices from MRI scans acquired for four selected cases. GTV_P, GTV_{10}, GTV_{20}, GTV_{30}, and GTV_{FU} contours are shown in red, green, blue, yellow, and purple, respectively. Patient numbers are referring to supplementary Fig. 1. *Patient 10* had a 19 cc tumour located in the right frontotemporal lope which had grown to 58 cc already by the 10th fraction. In the subsequent MRI scans, the tumour grew slightly larger – ending at 78 cc in MR_{FU}. By the 20th fraction, the GTV extended up to 20.6 mm from the surface of GTP_P, however, although the GTV by then was slightly outside the original CTV, it was decided not to adapt the plan because the target was still sufficiently covered by dose. *Patient 14* had a 25 cc tumour located in the right parietal lobe, which after a small decrease in volume at the 10th fraction (18 cc) the volume increased slightly in the subsequent fractions to 28 cc at MR_{FU}. Although the volume was stable during the treatment course, there was a considerable change in shape. Hence, by the 20th fraction, the GTV extended 11 mm from GTV_P. *Patient 19* had a 32 cc tumour in the right frontal lope, which initially seemed quite stable. However, by the 20th fraction, a new focus developed, extending the GTV up to 27 mm from GTV_P. The new focus was located within the CTV as it had been expanded to cover part of the hyperintense area on the T2/FLAIR scan outside the isotropic expansion of GTV_P and plan adaptation was therefore not necessary. During the rest of the treatment, the focus grew further, and the final volume of GTV_{FU} was 51 cc. *Patient 21* had a 34 cc tumour in the left parietal lobe which had a volume that was shrinking rapidly during treatment. By the 10th fraction, the volume was 22 cc. However, also for this patient, a new focus was developing, which meant that the GTV extended up to 12 mm from GTV_P by the 10th fraction. This new focus was located within the CTV and plan adaptation was therefore not necessary.

At fraction 10, the median D_{max} (range) was 5.7 (2.0–18.9) mm. This increased to 8.0 (2.0–27.4) mm, 8.0 (1.9–27.3) mm, and 8.9 (1.9–34.4) mm for GTV_{20}, GTV_{30}, and GTV_{FU}, respectively. The absolute change in D_{max} from the GTV_{10} to GTV_{20}, GTV_{20} to GTV_{30}, as well as from GTV_{30} to GTV_{FU} were all significantly smaller than the D_{max} at MR_{10} ($p < 0.001$). The population median and patient individual D_{max} is shown as a function of time in Fig. 3A. D_{max} does not change substantially after fraction 10 for most patients. Two patients had a D_{max} larger than 20 mm at fraction 20, but these patients did not require plan adaptation during RT as the GTVs were still sufficiently covered by dose.

The population median and patient individual R-GTV is shown as a function of time in Fig. 3B. Although the median R-GTV was stable over time, a large variation among the individual patients

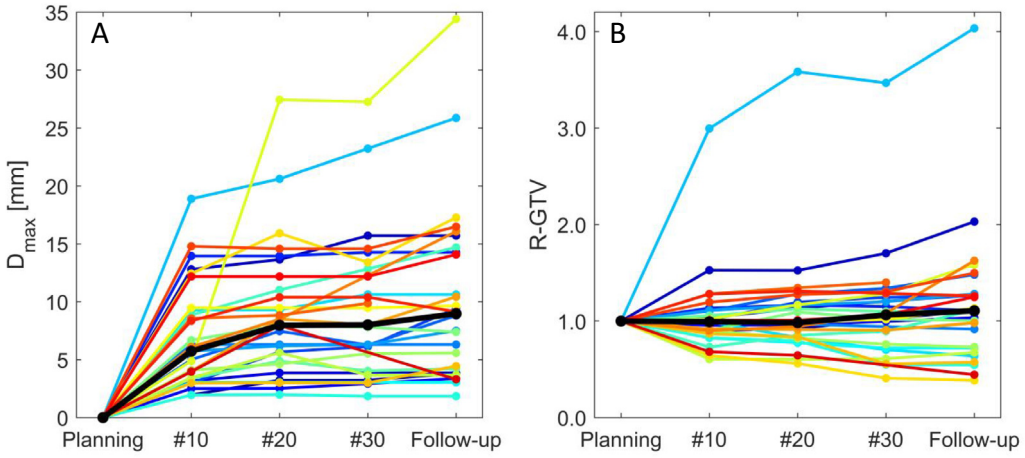

Fig. 3. (A) Median (black) and patient individual (colour code from supplementary Fig. 1) maximum extension distance (D_{max}) from any point on the GTV_X contour outside of GTV_P to the closest point on the GTV_P and (B) median and patient individual relative GTV volumes plotted for MRI scans acquired at different treatment fractions and follow-up.

was observed. In fifteen patients, the development in R-GTV was monotonic, whereas the remaining patients had both increases and decreases in R-GTV throughout the course. From time point to time point, the median absolute change in volume from MR_P to MR_{10} was 2.6 cc while it was 1.8 cc from MR_{10} to MR_{20}, 1.6 cc from MR_{20} to MR_{30}, and 1.1 cc from MR_{30} to MR_{FU}. Patient individual D_{max} and R-GTV including patient numbering is shown in supplementary Fig. 2.

There was a significant correlation ($R = 0.79$, $p < 0.001$) between D_{max} at fraction 10 and follow-up (Fig. 4A). The absolute GTV volume at planning was not related to the R-GTV at follow-up ($R = -0.19$, $p = 0.32$) (Fig. 4B). However, there was a significant correlation ($R = 0.74$, $p < 0.001$) between the R-GTV at fraction 10 and follow-up (Fig. 4C). Furthermore, there was a significant correlation ($R = 0.42–0.55$, $p < 0.05$) between R-GTV and D_{max} at all imaging time points.

Discussion

In the current study, a detailed investigation of the development of the GTV extent during RT in 29 GBM patients was performed. To the best of our knowledge, this study is the first to report on a clinical decision for RT plan adaptation to avoid geographical misses based on the actual GTV location during RT in a prospective trial. According to the prospective clinical evaluation, no patients needed plan adaptation after 10 or 20 treatment fractions to avoid geographical misses. However, this study reports large variations in GTV extent during the treatment course providing new knowledge for developing future adaptive RT strategies for patients with GBM.

The study shows that D_{max} was quite large already one-third through the treatment, and for many patients, it did not change substantially afterwards. The data show that D_{max} was more than 10 mm in seven (24%) and more than 20 mm in two (7%) patients two-thirds through treatment. This is less than the 53% and 27% in the study by Manon et al [19], who reported on 15 GBM patients, where MRI was performed during RT for the planning of a boost according to the Radiation Therapy Oncology Group (RTOG) guidelines [20]. Our results are in line with a very recent study by Stewart et al. [15] quantitating the interfraction target changes in 61 GBM patients during single phase RT. Their results show that the GTV migrate more than 10 mm in 20% and more than 15 mm in 6% of the patients during RT, although it should be mentioned that patients with multifocal disease foci at any time-point were excluded in their evaluation.

Although the actual GTV was covered by dose during the treatment course for the patients in the current study, it is not known whether patients with growing GTVs have a higher density of tumour cells located outside the original CTV border than patients without growing tumours. If the growing tumours infiltrate the geographical region surrounding the tumour in the latter stages of an RT course, geographical misses might have occurred in these patients. To avoid such potential underdosage of tumour cells, future RT trials could embrace a more aggressive plan adaptation strategy based on an expansion of the CTV from the actual GTV extent. Furthermore, for patients with shrinking tumours, pursuing such a strategy might lead to improved quality of life without compromising tumour control by adapting to a reduced treatment volume. Furthermore, if patients are treated with GTV-CTV margins smaller than the 20 mm standard margin used in the current study, the present data suggest that such reduced margins should be combined with interim T1w MR imaging to monitor the actual GTV extent in order to avoid geographical misses. Patients with GBM could therefore potentially be candidates for adaptive MR guided RT delivery on MR linacs [21–24], although the safety of use of contrast agents during RT delivery in the brain needs to be clarified.

Although a significant correlation between R-GTV and D_{max} was observed in the current study, the data also show that patients experiencing large maximal extent of the actual GTV outside the original GTV during treatment may simultaneously have reduced GTV volume (e.g. patient number 11 and 21 as seen in supplementary Fig. 2G and H). These data are in line with the findings of Stewart et al. [15]. In general, the current results show that although the median GTV volume did not change over time, a large interpatient variation was observed. Furthermore, the data shows that large absolute change in GTV volume occurs from the acquisition of the planning MR to the 10th treatment fraction. The early changes in tumour extent observed in the current study will favour early re-planning of patients if a more aggressive adaptation strategy is chosen in future trials.

Besides the recent study by Stewart et al. [15], previously published data on the change in tumour extent during RT is scarce. In a study including 11 patients with different gliomas (WHO grade 2, 3, and 4) receiving at least partial resection, Yang et al [11] reported that the volume of the residual tumour did not change

significantly, but shrinkage of the surgical cavity leads to a significant decrease of the GTV and dose to organ at risk. Inclusion of patients with WHO grade 2 and 3 gliomas make it challenging to compare with the current study, as the definition of the GTV differs according to the WHO grade [6,16,20]. Other groups also included both WHO grade 3 and 4 tumours [13,14] but opposed to the current study, the GTV was delineated according to the RTOG guidelines [20].

The largest study previously published was by Leitzen et al [10], who retrospectively reported on GBM patients having repeated MR imaging halfway through treatment and immediately after treatment completion. Based on these MR images, patients were categorised as having definite progression, questionable progression or no change according to the Response Assessment in Neuro-Oncology (RANO) criteria [25] although these criteria were developed for post-therapeutic imaging as mentioned by the authors. In their study, three patients fulfilled the criteria for pseudoprogression, defined as a new contrast-enhancing area that decreased on the next MRI. Pseudoprogression was originally described by de Wit et al [26], who reported that the first post-RT MRI showed an increased volume of contrast enhancement in 28% of the patients and that 33% of these patients stabilised radiologically and clinically at 6 months without further treatment. As reviewed by Thust et al. [27] pseudoprogression is still a well-known clinical challenge. Whether the increased volume of contrast enhancement observed in some patients in the current study was pseudoprogression or true progression will require further analysis on follow-up data and is out of the scope of the current study.

Interestingly, the current study has shown a strong correlation between the relative GTV volume at fraction 10 and follow-up, while the absolute volume of the GTV at planning was not related to the relative volume at follow-up. This raises the question of whether the relative GTV volume estimated already one third through the treatment may be used as a predictor for survival, which would allow for early stratification of patients into groups with modified therapy. In the study of Leitzen et al. [10], patients with progression halfway through treatment had a lower life expectancy compared with patients showing no change at that time point. The cohort investigated in the current study is not large enough for survival analysis, but data is currently being collected that would allow such exploration in the future.

A limitation of the current study was the use of patient-specific GTV-CVT margins in some cases. According to our local guidelines, a 20 mm expansion from the GTV to the CTV is recommended. However, in three cases the CTV margin was reduced due to large GTVs. Furthermore, in six cases the CTV was slightly extended to cover part of the hyperintense area on the T2/FLAIR scan outside the isotropic expansion, which is also recommended by the EANO guidelines [6]. In one of these patients, a new focus developed during RT, extending the GTV up to 27 mm from GTV_P at fraction 20 (see Fig. 2) and in this patient, dose coverage was only achieved due to the extension of the standard margin.

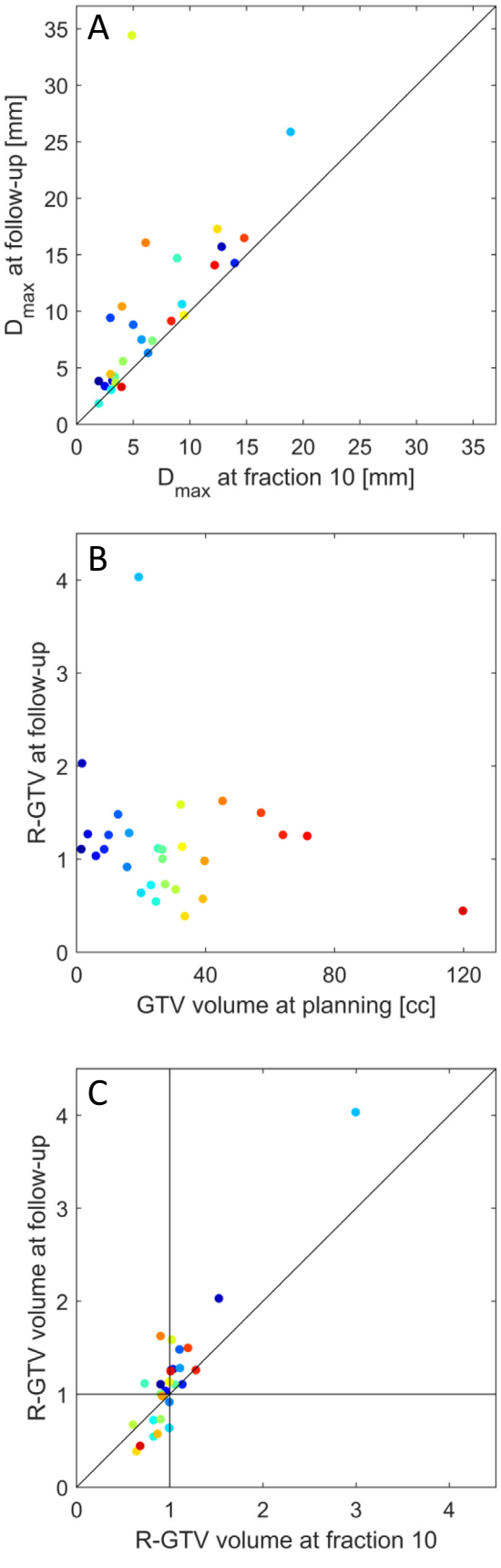

Fig. 4. (A) The maximum extension distance (D_{max}) from any point on the GTV_x contour outside of GTV_P to the closest point on the GTV_p contour plotted for GTV_{FU} as a function of D_{max} for GTV_{10}. Almost all data points lie close to or above the line of identity (black) showing that most patients had similar or larger D_{max} at follow-up compared to fraction 10. (B) Relativ GTV volume (R-GTV) at follow-up plotted as a function of the absolute GTV volume at planning. (C) R-GTV at follow-up plotted as a function of R-GTV at fraction 10. The line of identity, vertical and horizontal lines intersecting at unity are shown. Thirteen patients had R-GTV above baseline at fraction 10 and follow-up, six patients had R-GTV below baseline at fraction 10 but above baseline at follow-up, while 10 patients had R-GTV below baseline both at fraction 10 and follow-up. There are no patients in the lower right corner of the plot i.e. all patients having relative tumour volume above baseline at fraction 10 also had a relative tumour volume above baseline at follow-up. The colour code in all plots is from supplementary Fig. 1.

In summary, plan adaptation during the RT course was not needed to sufficiently cover the GTV with dose in the current cohort of GBM patients treated according to the EANO guidelines. However, a large variation in the GTV extent during the treatment course was observed, and many of the changes take place within the initial part of the treatment. The current data indicate that use of frequent interim MR imaging and a plan adaptation protocol is needed if a reduction of the GTV-CTV margin is implemented. A strong correlation between changes in the initial part of the treatment and at follow-up was observed. Whether such early changes carry prognostic value remains to be explored in future studies.

Conflict of Interest Statement

There are no known conflicts of interest associated with this publication.

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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.2021.04.001.

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