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Impact of clinical target volume margin reduction in glioblastoma patients treated with concurrent chemoradiation

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Abstract

Background. Glioblastoma (GBM) is widely treated using large radiotherapy margins, resulting in substantial irradiation of the surrounding cerebral structures. In this context, the question arises whether these margins could be safely reduced. In 2018, clinical target volume (CTV) expansion was reduced in our institution from 20 to 15 mm around the gross target volume (GTV) (ie, the contrast-enhancing tumor/cavity). We sought to retrospectively analyze the impact of this reduction.

Methods. All adult patients with GBM treated between January 2015 and December 2020 with concurrent chemoradiation (60Gy/2Gy or 59.4Gy/1.8Gy) were analyzed. Patients treated using a 20 (CTV_{20}, $n = 57$) or 15 mm (CTV_{15}, $n = 56$) CTV margin were compared for target volumes, dose parameters to the surrounding organs, pattern of recurrence, and survival outcome.

Results. Mean GTV was similar in both groups (ie, CTV_{20}: 39.7cm^3; CTV_{15}: 37.8cm^3; $P = .71$). Mean CTV and PTV were reduced from 238.9cm^3 to 176.7cm^3 ($P = .001$) and from 292.6cm^3 to 217.0cm^3 ($P < .001$), for CTV_{20} and CTV_{15}, respectively. As a result, average brain mean dose (D_{mean}) was reduced from 25.2Gy to 21.0Gy ($P = .002$). Significantly lower values were also observed for left hippocampus D_{mean}, brainstem $D_{0.03cc}$, cochleas D_{mean}, and pituitary D_{mean}. Pattern of recurrence was similar, as well as patient outcome, ie, median progression-free survival was 8.0 and 7.0 months ($P = .80$), and median overall survival was 11.0 and 14.0 months ($P = .61$) for CTV_{20} and CTV_{15}, respectively.

Conclusions. In GBM patients treated with chemoradiation, reducing the CTV margin from 20 to 15 mm appears to be safe and offers the potential for less treatment toxicity.

Keywords:

CTV | glioblastoma | margin

Glioblastoma (GBM) is the most common primary malignant brain tumor, affecting 3 to 5 people out of 100 000 each year.[1] The management of GBM is multimodal and includes maximal safe resection, radiotherapy (RT), and chemotherapy.[2]

With regard to RT, GBM is widely treated using large treatment margins (ie, 2–3 cm around the surgical cavity and the residual tumor) based on the observation that most tumor recurrences (ie, > 80%) occur within this area according to autopsy and imaging studies.[3] However, the optimal radiation target volume in GBM is still a matter of debate. Two main approaches currently coexist: The European guidelines[4,5] define the gross target volume (GTV) as the resection cavity plus any residual tumor on post-contrast T1-weighted MRI while the American guidelines (Radiation Therapy Oncology Group (RTOG)/ NRG)[6] recommend to also include any T2-FLAIR abnormalities (ie, the "peritumoral edema") in the GTV. According to both European and American approaches, a margin is then applied around the GTV to create the clinical target volume (CTV). The RTOG-NRG guidelines recommend using a CTV margin of 20 mm. Until recently, a 20 mm CTV margin was also recommended by the European guidelines (ie, European Society for Radiotherapy and Oncology (ESTRO)-ACROP guidelines published in 2016).[5] Besides the difference in target volume definition, European and American

approaches to RT in GBM also differ in the fact that the former recommends a single-phase treatment to 60 Gy in 30 fractions on the whole target volume, while the latter favors a two-phase treatment comprising a first phase until 46 Gy in 23 fractions on the whole target volume, followed by a cone-down boost delivering 14 Gy in 7 fractions of 2 Gy to the GTV to reach the total of 60 Gy.

Contouring according to the European guidelines (ie, not including the T2-peritumoral edema within the GTV) logically results in smaller treatment volumes than using the American recommendations. This should theoretically allow for less treatment toxicity but also carries the risk of higher recurrence rate. Based on this, Minniti et al. performed 2 retrospective recurrence pattern analyses in patients treated according to the 2016 ESTRO-ACROP guidelines. In the first one, they observed that most recurrences occur centrally/ in-field, and that using the larger RT volumes as proposed by the American guidelines would not lead to cover more recurrences.[7] In a second one, they observed that when recomputing a radiation treatment plan with a 10 mm CTV margin, the patterns of failure remained similar (ie, in the range of 85%–87% in-field failure).[8] The limitation of these retrospective analyses is that the observed pattern of recurrence could have been affected by the margin which was actually used to treat the patients (ie, 20 mm). Nevertheless, the European guidelines were recently updated and the recommended CTV margin was reduced from 20 to 15 mm.[4] However, no comparison between the outcome of patients treated with a 20 or 15 mm CTV margin is available yet.

In our institution, the CTV margin had already been reduced from 20 to 15 mm in 2018, based on an expert consensus in The Netherlands. In this context, we retrospectively analyzed the impact of this CTV reduction on treatment volumes, dosimetric parameters for the organs at risk (OARs), pattern of recurrence, and survival outcome.

Materials and Methods

Patients

This retrospective study included all adult patients with GBM treated with concurrent chemoradiation (with temozolomide, 75 mg/m2/day) at MAASTRO (Maastricht, The Netherlands) between January 2015 and December 2020. A total of 147 patients were retrieved. Patients treated with dose regimens other than 60 Gy in 30 fractions (60Gy/30#) or 59.4Gy/33# (eg, elderly regimen: 40Gy/15#) were excluded ($n = 23$), as well as patients treated with a CTV margin different than 20 or 15 mm ($n = 5$) and patients who did not complete RT ($n = 6$). Of the 113 remaining patients, 57 patients were treated using a CTV margin of 20 mm (CTV_{20} group), and 56 were treated using a CTV margin of 15 mm (CTV_{15} group) (Figure 1).

The study was conducted retrospectively from data obtained for clinical purposes and was approved by the Institutional Review Board (registration number P0477).

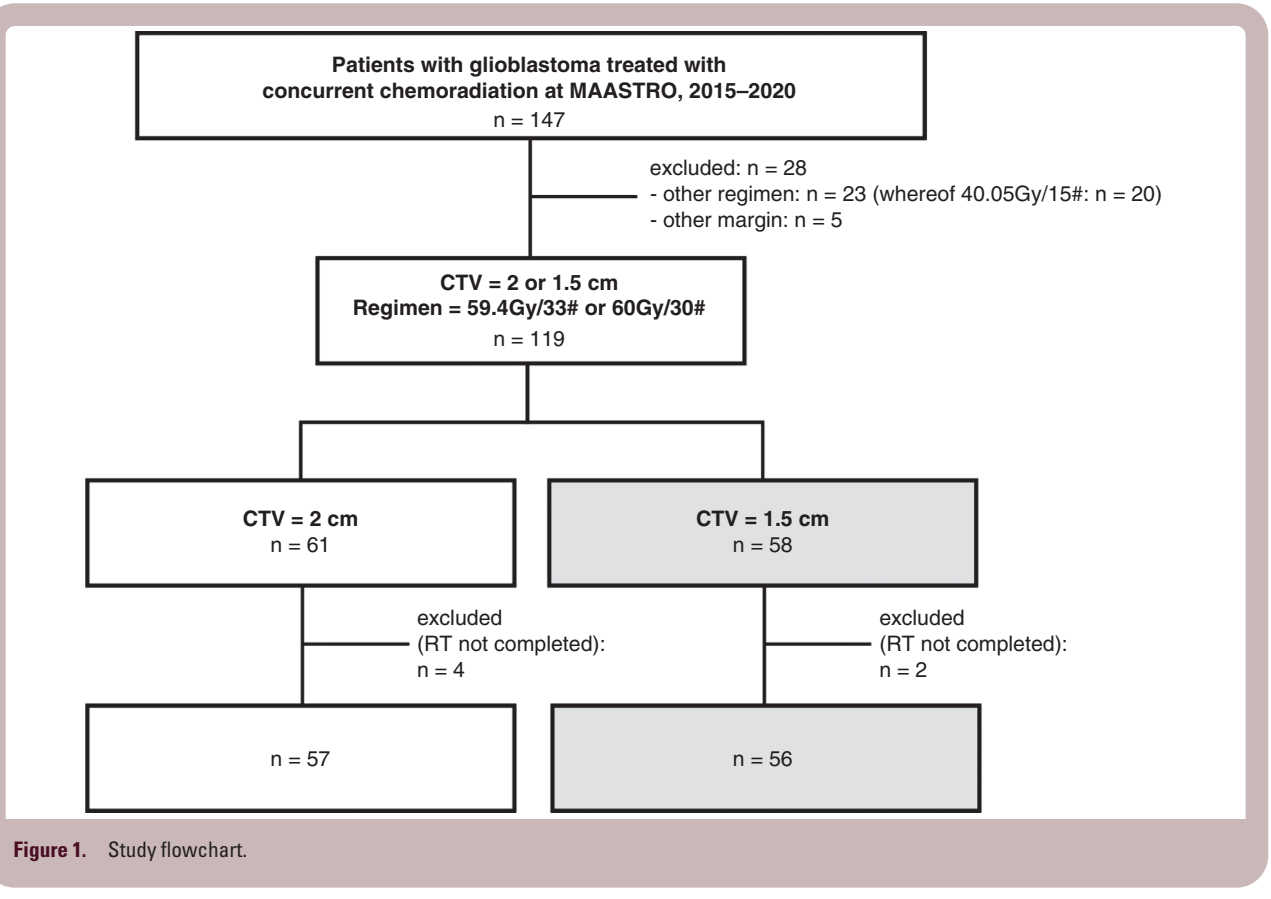


Figure 1. Study flowchart.

Treatment Volumes Delineation

For all patients, a simulation computed tomography (CT) scan was acquired in treatment position. Patients were immobilized using a thermoplastic mask. For delineation, the simulation CT was fused with a post-operative MRI scan (ie, post-contrast T1 and T2-FLAIR sequences). GTV was defined for all patients as the resection cavity plus any residual tumor (or the tumor for patients undergoing only a biopsy) based on the post-contrast T1 sequence. For the CTV_{20} group, CTV was created by adding a margin of 20 mm to the GTV (corrected based on anatomical barriers) and T2-FLAIR hyperintense regions were included in the CTV. For the CTV_{15} group, the CTV was generated using a margin of 15 mm around the GTV, and the T2-FLAIR hyperintense regions were included within 20 mm around the GTV. A PTV margin of 2 mm was further added (except for 4 patients in the CTV_{20} group who were treated using a 4 mm PTV margin). OARs were delineated as described in the European ParticleTherapy Network atlas for contouring in neuro-oncology.[9,10]

Follow-up

The first follow-up brain MRI scan was performed 4 months after RT, then repeated every 3 months. For all patients, the scans were reviewed for response assessment during the neuro-oncology tumor board. Tumor progression was defined based on the increase in size of the enhancing lesion or the apparition of new lesions.[11] Additional arguments in favor of progression were increased cerebral blood volume ratio on perfusion MRI or increased tracer uptake on amino acid PET imaging. In case of persisting ambiguity between true progression and pseudo-progression, progression was confirmed based on follow-up imaging and was backdated to the date of first evidence of radiological changes.

Treatment Plan Comparison

Treatment plans were compared between CTV_{20} and CTV_{15} patient groups with regard to target volumes (ie, GTV, CTV, and PTV volumes) and dose parameters to the OARs (ie, brain mean dose (D_{mean}), brainstem dose to 0.03cc ($D_{0.03cc}$), optic nerves $D_{0.03cc}$, optic chiasm $D_{0.03cc}$, cochleas D_{mean}, pituitary gland D_{mean}, and hippocampi D_{mean}).

Pattern of Recurrence Analysis

In patients with evaluable recurrences, the MRI showing tumor relapse was rigidly registered to the simulation CT. The recurrence was classified as *in-field*, *marginal*, or *distant* if ≥80%, 80%–20%, or ≤20% of the recurrent tumor volume was included in the PTV.

Statistical Analysis

In general, categorical variables are reported as counts and percentages and continuous variables are reported as mean and standard deviation or as median and interquartile range (IQR). Groups were compared using the chi-square test for categorical patient and tumor characteristics and the Student's *t*-test or Mann–Whitney U test for volumes and dose parameters. PFS (ie, the time from start of radiotherapy until progression or death, whichever occurs first) and OS (calculated from start of radiotherapy) were estimated using the Kaplan–Meier method, and curves were compared using the log-rank test. All tests were two-tailed and a *P*-value lower than .05 was considered as significant. Statistical analyses were performed using SPSS Statistical Software Version 27.0.1.0 (IBM, Armonk, NY, USA).

Results

Patient characteristics are described in Table 1. There was no difference between CTV_{20} and CTV_{15} groups based on age, sex, tumor side, MGMT methylation status, IDH mutation status, resection extent (debulking vs. biopsy only), or WHO performance status (Table 1).

In addition to temozolomide, 15 patients in CTV_{20} group and 5 patients CTV_{15} received other systemic treatments as part of clinical studies (ie, CTV_{20} group: Chloroquine [$n = 11$],[12] ABT414 (NCT02573324) [$n = 4$]; CTV_{15} group: Chloroquine [$n = 1$], marizomib (NCT03345095) [$n = 4$]).

There was no difference in GTV volume between patients in the CTV_{15} (mean: 37.8 cm^3) and in the CTV_{20} group (mean: 39.7 cm^3) ($P = .71$). Patients in the CTV_{15} group displayed significantly smaller CTV and PTV, ie mean CTV volume was reduced from 238.9 cm^3 to 176.7 cm^3 ($P < .01$) and mean PTV volume was reduced from 292.6 cm^3 to 217.0 cm^3 ($P < .01$) for the CTV_{20} and CTV_{15} groups, respectively (Table 1).

This translated into a significant reduction in the average brain D_{mean} (CTV_{20}: 25.2 Gy, CTV_{15}: 21.0 Gy, $P < .01$). This also led to a significantly lower median D_{mean} for the left hippocampus (CTV_{20}: 43.7 Gy, CTV_{15}: 10.6 Gy, $P = .04$), while there was no significant difference for the right hippocampus. Significantly lower values were also observed for the brainstem $D_{0.03cc}$, the right and the left cochleas D_{mean}, and the pituitary gland D_{mean} (Table 1). There was no significant difference for the other OARs (ie, the right and left optic nerves $D_{0.03cc}$, and the optic chiasm D0.03cc).

In total, recurrence was observed in 87 patients based on follow-up MRI (CTV_{20}: $n = 41$; CTV_{15}: $n = 46$). Of these, 75 were available for the pattern of recurrence analysis (CTV_{20}: $n = 38$; CTV_{15}: $n = 37$). Recurrence was predominantly observed *in-field* in both groups. In the CTV_{20} group, recurrence was *in-field* in 33 (86.8%), *marginal* in 4 (10.5%), and *distant* in 1 (2.6%) of the patients. Five out of thirty-three patients with *in-field* recurrences and 2 out of 4 patients with marginal recurrences presented simultaneously with distant recurrence (i.e., additional lesions distant from the initial tumor). In the CTV_{15} group, recurrence was *in-field* in 34 (91.9%), *marginal* in 2 (5.4%), and *distant* in 1 (2.7%) of the patients. Three out of thirty-four patients with *in-field* recurrences presented simultaneously with distant recurrence. For patients in the CTV_{15} group experiencing *marginal* or *distant* recurrences, the use of a 20 mm CTV would not have allowed for modifying the pattern of recurrence.

Table 1. Comparison of Patient Characteristics, Treatment Volumes, and OARs Dosimetric Parameters in the CTV_{20} and CTV_{15} Groups

		CTV_{20} group	CTV_{15} group	*P*
N		57	56	
Age (years)	median (range)	56.4 (33–70)	55.1 (25–70)	.47*
Sex (male)	*n* (%)	44 (77.2%)	37 (66.1%)	.22†
Tumor side (left)	*n* (%)	38 (66.7%)	31 (55.4%)	.25†
MGMT methylated	*n* (%)	29 (50.9%)	25 (44.6%)	.57†
IDH mutated	*n* (%)	4 (7.0%)	6 (10.7%)	.53†
Biopsy only	*n* (%)	19 (33.3%)	15 (26.8%)	.54†
WHO performance status - 0–1 - 2 - 3	*n* (%)	 42 (73.6%) 14 (24.6%) 1 (1.8%)	 44 (78.6%) 12 (21.4%) 0	.45†
GTV (cm^3)	mean ± SD	39.7 ± 29.0	37.8 ± 23.8	.71*
CTV (cm^3)	mean ± SD	238.9 ± 108.3	176. 7 ± 73.2	**.001***
PTV (cm^3)	mean ± SD	292.6 ± 124.1	217.0 ± 84.0	**<.001***
Brain D_{mean} (Gy)	mean ± SD	25.2 ± 7.8	21.0 ± 6.2	**.002***
Hippocampus R D_{mean} (Gy)	median (IQR)	11.8 (5.4–26.8)	7.1 (3.7–49.1)	.20‡
Hippocampus L D_{mean} (Gy)	median (IQR)	43.7 (6.7–59.2)	10.6 (6.0–51.8)	**.04‡**
Hippocampi D_{mean} (Gy)	median (IQR)	28.9 (14.7–34.9)	26.4 (5.4–32.6)	.13‡
Brainstem $D_{0.03cc}$ (Gy)	median (IQR)	58.8 (36.4–60.2)	54.1 (24.7–57.8)	**<.001‡**
Optic nerve R $D_{0.03cc}$ (Gy)	median (IQR)	21.6 (9.4–50.1)	17.4 (6.0–42.3)	.24‡
Optic nerve L $D_{0.03cc}$ c (Gy)	median (IQR)	34.5 (11.4–51.3)	16.0 (8.1–43.7)	.14‡
Optic chiasm $D_{0.03cc}$ (Gy)	median (IQR)	30.1 (15.8–53.3)	24.8 (9.3–53.9)	.37‡
Cochlea R D_{mean} (Gy)	median (IQR)	6.3 (1.8–13.4)	2.7 (0.8–8.4)	**.01‡**
Cochlea L D_{mean} (Gy)	median (IQR)	9.4 (2.8–29.8)	2.5 (0.9–11.1)	**.001‡**
Pituitary Gland D_{mean} (Gy)	median (IQR)	31.9 (7.9–40.3)	13.8 (2.4–26.5)	**.006‡**

**P*-value from *t*-test; †*P*-value from chi-square test; ‡*P*-value from Mann–Whitney test.
Abbreviations: L, left; R, right; D_{mean}, mean dose; $D_{0.03cc}$, dose to 0.03cc; OS, overall survival; PFS, progression-free survival; CTV, clinical target volume.

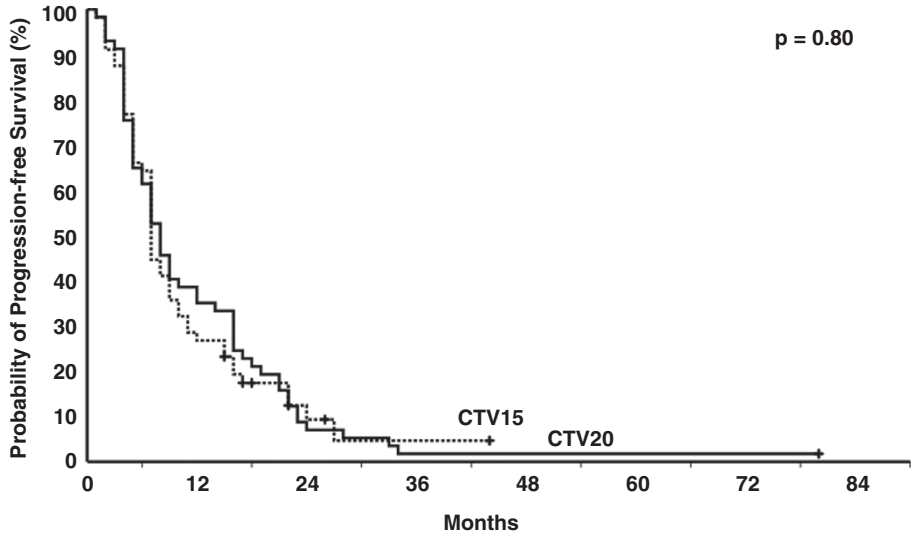
Both patient groups had similar outcome, ie, median PFS was 8.0 (95% CI: 6.2–9.8) and 7.0 months (95% CI: 6.3–7.7) ($P = .80$), and median OS was 11.0 (95% CI: 8.0–14.0) and 14.0 months (95% CI: 11.8–16.2) ($P = .61$) for CTV_{20} and CTV_{15}, respectively (Figure 2).

Discussion

We retrospectively analyzed the impact of reducing the CTV margin from 20 mm to 15 mm in GBM patients treated with concurrent chemoradiation. This reduction led to decreased radiation dose to the OARs without compromising the outcome of patients.

Several retrospective series have analyzed the outcome of glioblastoma patients treated with more limited margins (ie, total expansion, including both CTV and PTV, of 0.4–1.5 cm around the GTV).[13–15] After treatment, recurrence was mainly observed in-field, with no apparent increase in marginal failure, suggesting that such margin reduction is safe. In these studies, patients were treated based on the American approach (ie, for the first phase of the treatment, the GTV includes the T2-FLAIR hyperintense region).

A recent phase 2 randomized study compared the outcome of patients treated according to the American (RTOG) guidelines to a hybrid strategy (ie, The University of Texas MD Anderson Cancer Center (MDACC) guidelines) resembling the European approach. MDACC treatment guidelines are similar to the 2016 ESTRO-ACROP in terms of treatment volume (ie, the peritumoral edema is not included in the GTV and the CTV expansion for the first phase of the treatment is 20 mm) but include a boost-phase. In this study, the MDACC approach led to improved PFS and OS, as well as to improved quality of life (QOL).[16] This improvement is attributed to the fact that smaller treatment volumes lead to lower doses to the surrounding brain structures and thereby to lower toxicity. This is in line with recent data showing that cranial radiotherapy is associated with dose-dependent atrophy throughout the entire brain[17,18] and may be associated with cognitive impairment,[19] as well as with worse patient-reported outcomes (ie, health-related QOL and self-reported cognitive function).[20] Consequently, further decreasing the CTV expansion from 20 mm to 15



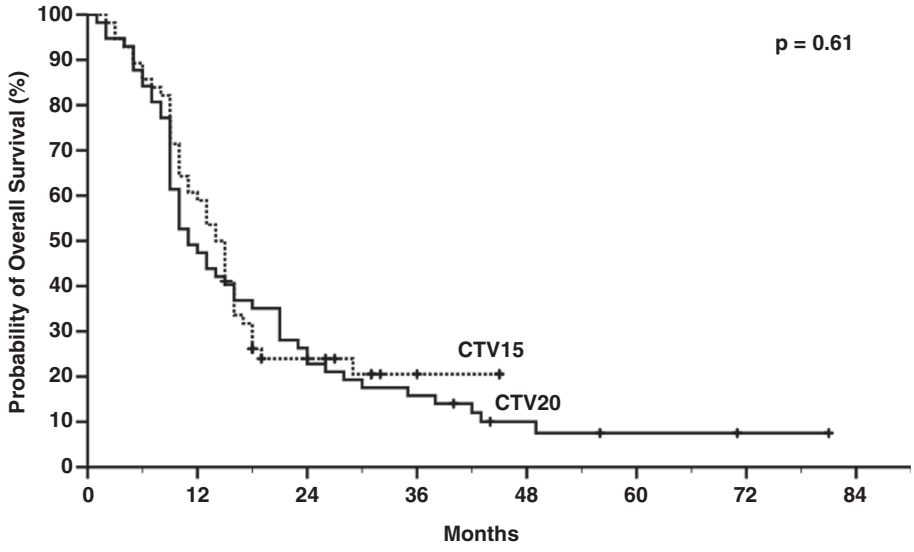


Figure 2. Kaplan–Meier estimates of progression-free survival and overall survival for patients treated with a clinical target volume (CTV) margin of 15 mm (CTV15) or 20 mm (CTV20).

mm as in our patient cohort and as recommended by the new European guidelines[4] may allow for further improvement in the toxicity profile of the treatment.

In the future, even more radical reductions in RT treatment margins may be envisaged. In this context, 2 potential issues should be considered, namely anatomical changes and contouring variations. First, as treatment margins become smaller, anatomical variations during treatment become more critical. In a recent study, Stewart et al.[21] performed repeated MR imaging during chemoradiation and observed a displacement of the GTV or more than 5 mm and 10 mm in 58% and 26% of the patients, respectively. This issue could be overcome with adaptive RT (ART).[22] The use of a limited CTV margin of 5 mm in conjunction with MR-based ART is evaluated in the UNITED trial (NCT04726397). Second, with more limited treatment margins, contouring accuracy becomes even more crucial.

A preliminary analysis of the interobserver delineation variability for the benchmark case in the EORTC-1709-BTG trial (i.e. evaluating the addition of marizomib to temozolomide chemoradiation) showed that 53% of the submitted cases required adjustments in contouring, mostly due to inaccuracies in target volume delineation (e.g. missing parts in the GTV).[23]As these inaccuracies could in turn have an impact on treatment outcome, efforts should be made to minimize them (e.g. comprehensive delineation guidelines, double-review of contours).

Limitations of the present study include its retrospective character and the fact that clinical evaluation of the

patients (eg, acute and late toxicities, QOL, and cognitive function) during and after treatment is not reported.

In summary, reducing the CTV margin from 20 to 15 mm in GBM patients treated with chemoradiation appears to be safe and offers the potential for less treatment toxicity.

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Conflict of interest statement

None.

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