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# Reducing clinical target volume margins for multifocal glioblastoma: a multi-institutional analysis of patterns of recurrence and treatment response

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**Purpose:** No guidelines exist to delineate radiation therapy (RT) targets for the treatment of multiple glioblastoma (mGBM). This study analyzes margins around the gross tumor volume (GTV) to create a clinical target volume (CTV), comparing response parameters and modalities of recurrence.

**Material and Methods:** One-hundred and three mGBM patients with a CTV margin of 2 cm (GTV + 2.0 cm) or 1 cm (GTV + 1.0 cm) were retrospectively analyzed. All patients received a total dose of 59.4–60 Gy in 1.8–2.0 Gy daily fractions, delivered from 4 to 8 weeks after surgery, concomitantly with temozolomide (75 mg/m$^2$). Overall survival (OS) and progression-free survival (PFS) were calculated from the date of surgery until diagnosis of disease progression performed by magnetic resonance imaging and classified as marginal, in-field, or distant, comparing site of progression with dose distribution in RT plan.

**Results:** OS in mGBM CTV1 group was 11.2 months (95% confidence interval [CI], 10.3–12.1), and 9.2 months in mGBM CTV2 group (95% CI, 9.0–11.3). PFS in mGBM CTV1 group occurred within 8.3 months (95% CI, 7.3–9.3), and 7.3 months in mGBM CTV2 group (95% CI, 6.4–8.1). No difference was observed between the two groups in terms of OS and PFS time distribution. Adjusted to a multivariate Cox risk model, epidermal growth factor receptor amplification resulted a negative prognostic factor for both OS and PFS.

**Conclusion:** In mGBM, the use of a 1 cm CTV expansion seems feasible as it does not significantly affect oncological outcomes and progression outcome.

**Keywords:** Multifocal glioblastoma, Radiotherapy delineation, Clinical target volume, Recurrence patterns

## Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumor with a median overall survival (OS) of 3 months in untreated patients and approximately of 14 months in patients treated with a surgery-based multimodality approach [1-4].

GBM usually presents on imaging as a single peripherally enhancing lesion even though multiple enhancing lesions may occur, resulting in a poorer prognosis. Multiple GBMs (mGBMs) are distinguished as multifocal or multicentric depending on whether a macroscopic and/or microscopic connection between the uptake lesions can be demonstrated. Notably, there is no significant difference in the management of unifocal or multiple GBM [5-12], despite what has recently been suggested that personalized therapies should be used in these patients [13].

External beam radiotherapy (RT) plays a crucial role in the treatment of GBM, resulting an integral part of the multimodal primary therapy of GBM. Thus, after the maximal safe debulking of the tumor, standard therapy for GBM patients up to age 70 with good performance status is a total dose of 60 Gy in 30–33 fractions, 180–200 cGy per day, with the addition of concurrent and adjuvant temozolomide chemotherapy [4]. Hypofractionated RT, 40 Gy in 15 fractions, 266 cGy per day, can be used for patients older than 70 years or with poor performance status [14]. Notably, the spread of clonogenic GBM cells far from the gross tumor volume (GTV) has been shown to be responsible for the persistent tumor recurrence [15-23]. Thus, the current standard approach to define the clinical target volume (CTV) for RT of unifocal GBM involves the application of a margin of 1–1.5 cm around the GTV, which is reduced compared to previous indications of 2–3 cm [24,25]. This allowed us to mitigate the cognitive consequences of RT on healthy brain tissue, without compromising the survival advantages established by standard chemoradiotherapy [24,25]. However, specific indications for mGBM are lacking, and CTV margins of 2–3 cm are most frequently used [5,26].

In this study, we aimed to retrospectively analyze a cohort of mGBM patients, dividing them into two subgroups based on CTV margins of 2 cm or 1 cm. The purpose of this research is to compare the oncological outcomes and progression patterns between these two distinct groups.

## Materials and Methods

### 1. Study design and patients

Patients with primary diagnosis of a multifocal growth pattern GBM, who underwent RT at the Department of Radiotherapy of Le Scotte Hospital, Siena (Italy) and Policlinico Umberto I, Rome (Italy) between January 2016 and December 2022 were retrospectively analyzed. Only patients with (1) histologically confirmed GBM exhibiting a multifocal growth pattern at the time of initial diagnosis and (2) pre- and post-RT magnetic resonance imaging (MRI) with contrast enhanced T1 and T2 or fluid attenuated inversion recovery (FLAIR) sequences were included. The presence of a multifocal growth pattern was evaluated by an experienced neuroradiologist. This pattern was defined as the existence of at least two separate areas with enhanced contrast in the MRI T1 contrast-enhanced sequence. To be included in the study, patients had to have undergone chemoradiotherapy within 4–8 weeks after surgery (partial or complete resection) based on the Stupp protocol [4]. Additionally, MRI imaging of the tumor recurrence at the time of analysis was required. Patients were excluded from the study if their Karnofsky performance scale (KPS) score was below 60, if they had undergone previous whole brain radiation therapy, or if their tumor histology did not confirm GBM. The $O^6$-methylguanine-DNA-methyltransferase (MGMT) promoter methylation status and epidermal growth factor receptor (EGFR) amplification status, available for all patients selected for this analysis, were assessed by using a methylation-specific polymerase chain reaction (PCR). Briefly, genomic DNA was extracted from paraffin-embedded tumor sections and treated with sodium bisulfite using the EZ DNA Methylation-Gold kit (HISS Diagnostics GmbH, Freiburg, Germany). Primer sequences were used to detect methylated and unmethylated MGMT promoter sequences. PCR products were separated on 2% agarose gel. A glioma cell line with a completely methylated MGMT promoter, and peripheral blood mononucleated cells, served as positive and negative control samples, respectively [27,28]. A methylation percentage of 5% was used as a cut-off value: samples with methylation $<5\%$ and $>5\%$ were classified as unmethylated (unmetMGMT) and methylated (methMGMT), respectively. This study was approved by the Institutional Review Board of "Le Scotte" Hospital of Siena (No. 2023-01-001). All patients signed informed consent to participate in the study.

### 2. Radiotherapy protocol

All patients were provided with an individual thermoplastic mask to ensure that patient positioning during planning computed tomography (CT) and subsequent RT sessions were reproducible. For treatment planning, a CT was conducted using sections that were 2.5/3 mm thick. CT images were then co-registered with gadolinium contrast medium enhanced T1 sequences obtained from a diagnostic MRI. To delineate treatment volumes, MRI T1 contrast-enhanced sequence scans were used, along with FLAIR sequences to identify grossly visible lesions such as the GTV. The CTV consisted of the GTV along with a 1 cm margin (CTV1) or a 2 cm margin (CTV2)


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to account for microscopic tumor spread and perifocal edema that was visible on the T2 or FLAIR sequence. T2 FLAIR abnormality beyond the delineated CTV1 and CTV2 was not intentionally included in the CTV [4]. The primary determinant influencing CTV margin selection was the amount of macroscopic disease lesions, as typically a greater number of lesions requires the use of a narrower margin to mitigate irradiation of healthy brain tissue. However, the choice to use a more or less wide CTV was always at the discretion of the radiation oncologist.

The margins surrounding the CTV were minimized to 1–3 mm around natural barriers impeding tumor growth (skull, ventricles, sickle). This reduction was implemented to ensure the preservation of the optic nerve and chiasm. The CTV was subsequently expanded by 3–5 mm to generate the planning target volume (PTV) in adherence to setup protocols. The prescribed dose was normalized to the 100% isocenter, ensuring that the 95% isodose area adequately covered the PTV (ICRU Report 50 [4]). The maximum allowable doses for the organs at risk were specified as follows: brainstem (D < 54 Gy), optic nerves (D < 54 Gy), chiasm (D < 55 Gy), eyes (Macula < 45 Gy), cochlea (D < 45 Gy), and lens (D < 6 Gy) [4]. Radiation treatment plans were generated using three-dimensional conformal RT (3DCRT), intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT). RT consisted of fractionated irradiation at a dose of 59.4–60 Gy divided into fractions of 1.8-2.0 Gy each (median total dose 60 Gy; median fractional dose 2 Gy; median number of fraction 30), plus concomitant 75 mg/m$^2$ of temozolomide [4]. Simultaneous integrated boost or field reduction was not used in any patient. Adjuvant temozolomide was began 4 weeks after the completion of RT and was continued for 5 consecutive days every 28 days for a maximum of 12 cycles. In the first cycle of adjuvant chemotherapy, temozolomide was administered at a dosage of 150 mg/m$^2$, which was then escalated to 200 mg/m$^2$ starting from the second cycle

### 3. Response evaluation and pattern of relapse

The MRI was conducted approximately 30 days after completion of RT, and then repeated every 12 weeks or as necessary depending on the individual's neurological status. The radiological response was assessed using the Response Assessment in Neuro-Oncology (RANO) criteria [25].

Tumor progression was defined if a growth of more than 25% in tumor size was observed or the appearance of a new lesion on the imaging scans. Two separate MRI evaluations, with at least a 2-month interval between them, were required to confirm radiological tumor progression. Tumor progression was recorded at the time of the first MRI showing progression. The imaging data set for the study of tumor progression consisted of post-contrast T1-weighted MRI and FLAIR MRI imaging. All MRI datasets were recorded alongside planning CT and compared with the pretreatment MRI. Progression was categorized as "in-field" if more than 80% of the intersection area was covered by the 95% isodose line, "marginal" if 20%–80% of the intersection region fell within the 95% isodose line, or "distant" if less than 20% of the volume was within the 95% isodose line. The mean dose received by 50% of the brain volume was compared between the plans [29].

### 4. Outcome study measures

The progression-free survival (PFS) and OS were used as key study outcome measures. PFS was defined as the time from initial surgery to the occurrence of the first radiological progression, as determined by MRI according to the RANO response assessment criteria [30,31]. OS was defined as the time elapsed between the date of the initial surgery and either the patient's death from any cause or the last known date when the patient was confirmed to be alive.

### 5. Statistical analysis

The investigated variables were analyzed using descriptive statistics. Continuous variables were normally distributed according with the Shapiro-Wilk test and were summarized as means and 95% confidence interval (CI) and compared using Student t-test. Nominal variables were summarized as absolute and relative frequencies and compared using the Pearson chi-square test, as appropriate. PFS and OS were estimated using the log-rank test (Kaplan-Meier method). Multivariate survival analysis was performed using the Cox regression model. A significance level of $p < 0.05$ was considered statistically significant. Data collection and analysis were conducted using IBM SPSS Statistics (version 21; IBM Corp., Armonk, NY, USA).

## Results

This analysis included a total of 103 patients with mGBM, after excluding those who had previous radiation treatment or histotypes other than GBM or had not histologically proven GBM. The mean age of the entire population was 63.1 years (95% CI, 60.5–65.5). The mean age for the mGBM CTV1 group was 62.1 years (95% CI, 60.3–65.3), while for the mGBM CTV2 group it was 63.4 years (95% CI, 56.4–63.5), with no significant difference between the two groups ($p = 0.760$). The mean follow-up for the entire population was 9.9 months (95% CI, 9.2–10.6). Regarding the initial surgery, gross resection was performed in four patients (3.9%), subtotal in 54 patients (52.4%), and stereotactic biopsy in 45 patients (43.7%). A summary of patient characteristics can be found in Table 1, and a representative contouring example of the two CTVs is

**Table 1.** Summary of patient characteristics

| Variable | mGBM CTV1 group (n = 54) | mGBM CTV2 group (n = 49) | p-value |
|---|---|---|---|
| Age (yr) | 62.8 (60.3–65.3) | 63.3 (60.7–66.1) | 0.760 |
| Karnofsky performance status | 78.5 (75.8–81.2) | 82.6 (79.8–85.5) | 0.038 |
| Extent of surgery | | | 0.600 |
| Gross total | 4 (7.4) | 0 (0) | |
| Subtotal | 26 (48.2) | 28 (57.1) | |
| Biopsy | 24 (44.4) | 21 (42.9) | |
| Number of lesions | 2.8 (2.6–3.1) | 3.3 (3.0–3.5) | 0.013 |
| MGMT status | | | 0.090 |
| Methylated | 18 (33.3) | 22 (44.9) | |
| Unmethylated | 36 (66.7) | 27 (55.1) | |
| EGFR amplification | | | 0.004 |
| Yes | 33 (61.1) | 43 (87.7) | |
| No | 21 (38.9) | 6 (12.3) | |
| Concomitant TMZ | | | 1.000 |
| Yes | 54 (100) | 49 (100) | |
| No | 0 (0) | 0 (0) | |
| Adjuvant TMZ | | | 0.570 |
| Yes | 37 (68.5) | 37 (75.5) | |
| No | 17 (31.5) | 12 (24.5) | |
| CTV | 231.9 (209.6–254.1) | 271.8 (248.5–295.2) | 0.016 |

Values are presented as mean (95% confidence interval) or number (%).
mGBM, multifocal glioblastoma; CTV, clinical target volume; MGMT, $O^6$-methylguanine-DNA-methyltransferase; EGFR, epidermal growth factor receptor; TMZ, temozolomide.

presented in Fig. 1. Significant differences between the two study groups were observed in terms of EGFR amplification, number of tumor lesions, KPS and CTVs. Specifically, group mGBM CTV1 demonstrated a CTV of 231.9 $cm^3$ (range, 209.6 to 254.1 cm3) compared to 271.8 $cm^3$ (range, 248.5 to 295.2 $cm^3$) in the other group ($p = 0.016$). This finding indicates a potential reduction in irradiation volume within the group with reduced CTV margin. The dose-volume distribution in normal brain in patients undergoing localized external beam RT was assessed. The mean dose received by 50% of the brain volume was 18.5 Gy (95% CI, 17.7–19.4) in the CTV1 group and 22.4 Gy (95% CI, 21.7–23.1) and in CTV2 group, respectively. A significant reduction in the mean dose received by 50% of the brain volume was observed between the two groups ($p < 0.001$).

The pattern of progression was comparable with no statistically significant difference ($\chi^2 = 1.078$; degrees of freedom = 2; $p = 0.580$) between the two groups. Both in the mGBM CTV1 group (54 patients), and in CTV2 group (49 patients) all patients experienced progression. In the mGBM CTV1 group 77.8% (42 out of 54) experienced in-field, 9.3% (5 out of 54) marginal, and 13.0% (7 out of 54) distant progression. In the mGBM CTV2 group, 73.5% (36 out of 49) experienced in-field, 12.2% (6 out of 49) marginal, and 14.3% (7 out of 49) distant progression (Table 1).

An explorative analysis was performed to assess the potential relationship between the extent of surgical resection and the frequency of in-field, marginal, and distant progression within the two study groups.

In the mGBM CTV1 group, 44.4% patients (24 out of 54) exclusively underwent biopsy, then experiencing 62.5% patients (15 out of 24) in-field, progression, 16.6% patients (4 out of 24) marginal progression, and 20.8% patients (5 out of 24) distant progression. Subtotal resections were performed on 48.1% patients (26 out of 54) who then experienced 92.3% of cases (24 out of 26) in-field progression, 3.8% of cases (1 out of 26) marginal progression, and 3.8% of cases (1 out of 26) distant progressions. Gross total resection was performed on 7.4% patients (4 out of 54), 75.0% of them (3 out of 4) then experiencing in-field progressions and 25.0% (1 out of 4) distant progression. In the mGBM CTV2 group, 42.8% of cases (21 out of 49) underwent biopsy, then experiencing 71.4% (15 out of 21) in-field progression, 14.3% (3 out of 21) marginal progression, and 14.3% (3 out of 21) distant progression. Subtotal resections were performed on 57.1% of patients (28 out of 49), then all (28 out of 28) experiencing in-field progressions. No gross total resections were performed in this group. Pearson chi-square test was utilized to analyze these data. No significant difference was found between the extent of surgical resection and the occurrence of in-field, marginal, and distant progression, even when patients were classified based on CTV margins (Table 2).

The median OS in mGBM CTV1 group was 12.0 months (95% CI, 10.0–13.0), wherea mGBM CTV2 group had a mean OS of 11.8

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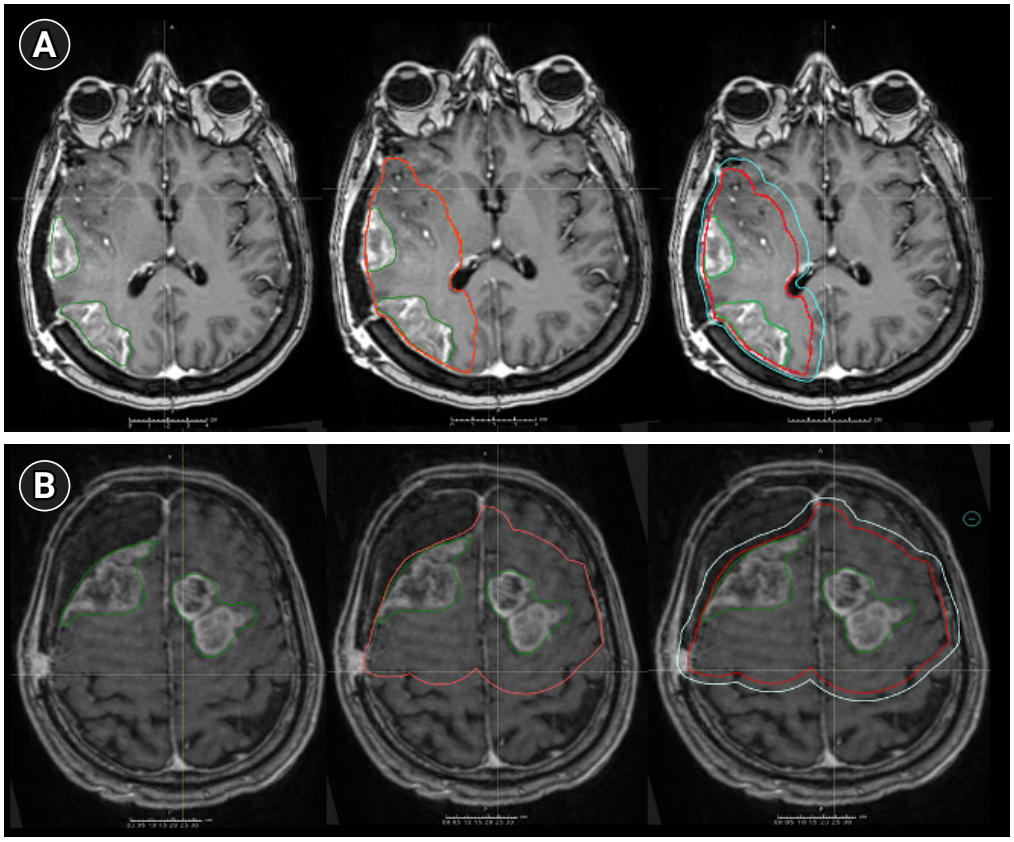


**Fig. 1.** Representative contouring of a patient affected by multifocal glioblastoma treated with 1 cm margin of CTV (A) and with 2 cm margin of CTV (B). mGBM, multifocal glioblastoma; Gross tumor volume (green line); CTV, clinical target volume (red line); Planning target volume (cyan line).

**Table 2.** Pattern of relapse according surgery extent (Pearson chi-square test)

| Extent of surgery | mGBM CTV1 group (n = 54) | | | p-value | mGBM CTV2 group (n = 49) | | | p-value |
|---|---|---|---|---|---|---|---|---|
| | Gross total (n = 4) | Subtotal (n = 26) | Biopsy (n = 24) | | Gross total (n = 0) | Subtotal (n = 28) | Biopsy (n = 21) | |
| In-field progression | 3 | 24 | 15 | | 0 | 28 | 15 | |
| Marginal progression | 0 | 1 | 4 | | 0 | 0 | 3 | |
| Distant progression | 1 | 1 | 5 | 0.070 | 0 | 0 | 3 | 0.100 |

mGBM, multifocal glioblastoma; CTV, clinical target volume.

months (95% CI, 10.0–13.0) (Fig. 2). In terms of PFS, mGBM CTV1 group had a mean PFS of 7.2 months (95% CI, 6.0–8.0), while mGBM CTV2 group had a mean PFS of 6.7 months (95% CI, 6.0–8.0) (Fig. 3). No statistically significant difference was observed between the two groups for OS (Fig. 2) and PFS (Fig. 3) time distribution. To further explore these results, we conducted a multivariate Cox risk model analysis adjusting for known variables such as age, MGMT methylation, EGFR amplification, number of tumor lesions, KPS score, and type of surgery. Our analysis revealed that both OS and PFS (Table 3) were associated with MGMT status and KPS. For OS, we had a hazard ratio (HR) of 1.71 (95% CI, 1.06–2.73; p = 0.023), and the unmetMGMT status had a HR of 1.52 (95% CI, 1.03–2.92; p = 0.036) indicating an increased risk of mortality. Similarly, in terms of PFS, the KPS <70 and the unmetMGMT status had an HR of 1.88 (95% CI, 1.21–2.94; p = 0.006) and 1.95 (95% CI, 1.11–3.01; p = 0.016) further supporting its prognostic significance (Table 3).

## Discussion and Conclusions

Despite the generally poorer prognosis associated with mGBM when compared to unifocal GBM [5-10], there is a lack of specific guidelines regarding the management approaches for this clinical entity. Specifically, the controversy regarding the role of surgical

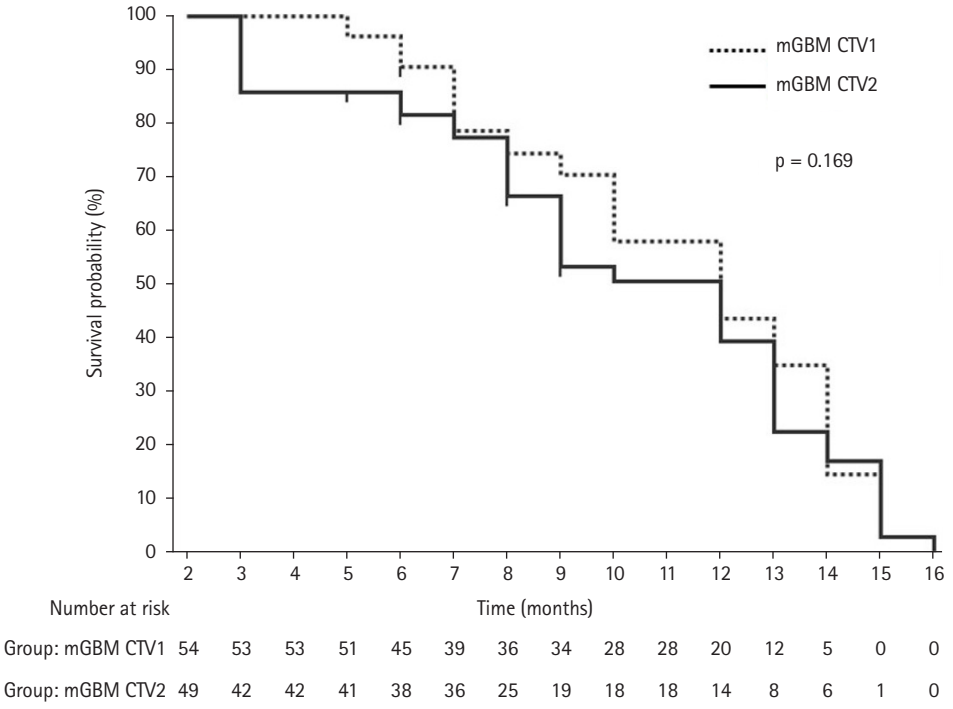


**Fig. 2.** Overall survival curve. mGBM, multifocal glioblastoma; CTV, clinical target volume.

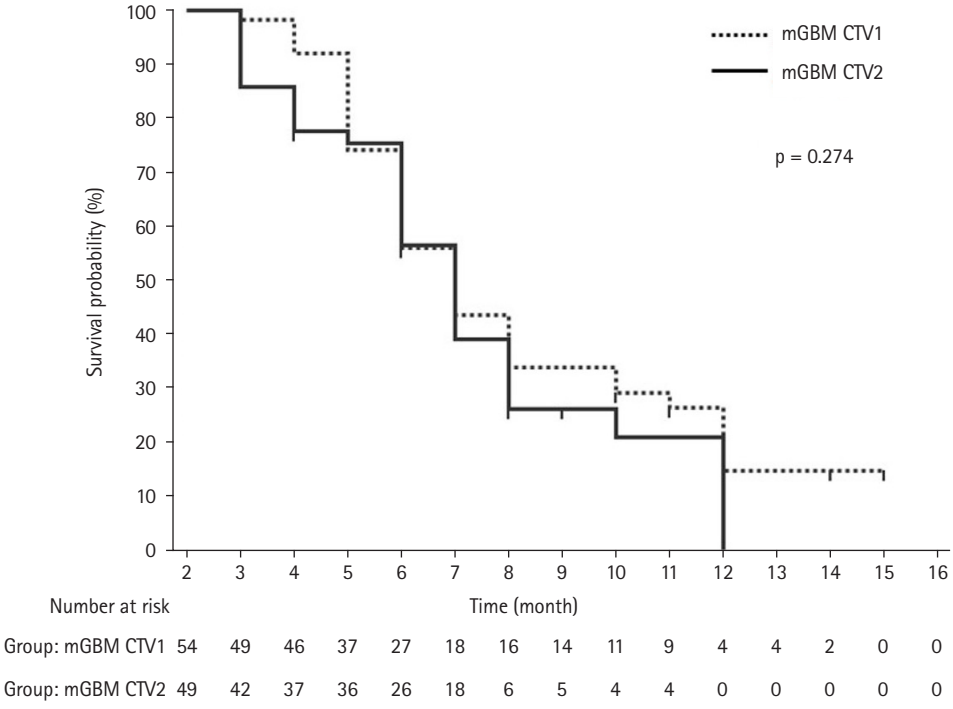


**Fig. 3.** Progression-free survival curve. mGBM, multifocal glioblastoma; CTV, clinical target volume.

treatment in mGBM [5-10] is in contrast with the confirmed efficacy of concomitant RT and temozolomide as a treatment option [4-10]. Nevertheless, there is a lack of clear guidelines regarding the precise target delineation for RT in mGBM. Indeed, whether the CTV for unifocal GBM has been recently defined as a 1–1.5 cm margin around the GTV [24,25], a margin of 2–3 cm is still applied around the GTV of mGBM [5,26], despite the most common pattern of treatment is central "in-field" relapse [32], similarly to unifocal

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**Table 3.** Univariate (OS) and multivariate Cox proportional-hazards regression analysis (OS, PFS)

| | Univariate | | Multivariate | | | |
|---|---|---|---|---|---|---|
| | OS | | OS | | PFS | |
| | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) |
| KPS | 0.038 | 0.53 (0.29–0.96) | 0.022 | 0.51 (0.28–0.90) | 0.005 | 0.44 (0.24–0.78) |
| MGMT status | 0.051 | 0.75 (0.56–0.99) | 0.035 | 0.74 (0.56–0.97) | 0.016 | 0.71 (0.55–0.93) |
| CTV | 0.662 | 1.00 (0.99–1.00) | 0.692 | 1.04 (0.97–1.06) | 0.440 | 0.99 (0.99–1.00) |
| EGFR amplification | 0.610 | 1.12 (0.70–1.79) | 0.778 | 1.09 (0.72–1.64) | 0.078 | 0.78 (0.53–1.03) |
| Number of lesions | 0.392 | 1.01 (0.98–1.03) | 0.425 | 1.10 (0.97–1.05) | 0.221 | 1.02 (0.98–1.08) |
| GTV | 0.952 | 0.99 (0.92–1.07) | 0.978 | 1.00 (0.96–1.08) | 0.876 | 0.96 (0.92–1.04) |

OS, overall survival; PFS, progression-free survival; KPS, Karnofsky performance scale; MGMT, $O^6$-methylguanine-DNA-methyltransferase; CTV, clinical target volume; EGFR, epidermal growth factor receptor; GTV, gross tumor volume; OR, odds ratio; CI, confidence interval.

GBM [33-35]. Thus, in clinical practice the factor that mainly determines the choice of the CTV margin is the quantity of macroscopic lesions since, to mitigate the irradiation of healthy brain tissue, a greater number of lesions generally requires the use of a margin closer.

Based on these findings gathered on unifocal GBM, we made the decision to explore, for the first time, the feasibility of reducing treatment volume delineation margins from 2 cm to 1 cm in mGBM. The purpose of this investigation was to evaluate the feasibility of implementing such a reduction comparing the progression patterns, PFS, and OS rates in this context.

Our study suggested that minimizing the CTV margin to 1 cm in mGBM may have no significant impact on the speed of progression patterns, as well as PFS and OS. It is noteworthy that many tumor progressions were observed within the treatment field with no difference between the two groups. This evidence confirms early studies on patterns of failure in unifocal GBM indicated that 70%–90% of recurrent lesions occurred within 2–3 cm of the primary tumor, even after whole-brain RT [33-35]. Several authors have suggested that these early studies come with several limitations that are inherent in their design. Firstly, the data in these studies was based on early-generation CT technology, which has lower image resolution compared to MRI [36]. Secondly, the assessment of recurrences required laborious manual detection between the radiation plan and subsequent imaging, and usually only one or a few slices were selected to measure two-dimensionally, rather than in three dimensions [37]. New evidence from recent studies indicates that 94.8% local recurrences occurred within 0.5–1 cm of the original T1 enhanced lesions [22,38] supporting the use of a reduced CTV margin of 1 cm in reducing the volume of irradiation. Our study also supports this evidence, as we were able to achieve a substantial reduction in the volume of CTV without affecting the PFS, the OS and the rate of progression patterns. Interestingly, no relationship was found between the extent of surgical resection and the frequency of in-field, marginal or distant progression in our study. This finding is consistent with other studies on unifocal GBM, even though it is in contrast with most previous studies that have reported a longer PFS with the gross tumor resection [39]. However, based on these results, we suggested adopting a reduced CTV margin for mGBM, regardless of the degree of resection achieved.

Our study has several limitations. One limitation is the possible presence of selection bias, which can be attributed to the retrospective nature of the study and the absence of prospective randomization in the two delineation of CTV modalities. The lack of information on the mutational status of iDH1, essential for a correct diagnostic/prognostic classification [40], but not available for all patients in our cohort, represented another limitation.

The small sample size restricted the number of variables analyses. Although we have conducted a multivariate Cox regression analysis, it is important to acknowledge that our study results may be influenced by variables beyond those considered in our analysis. The small sample size may also explain why in this study tumor resection status, a factor known to be significantly associated with PFS and OS [41], was not significantly associated with outcome. This may have generated the lack of significance in the difference in outcome based on the CTV margin.

Furthermore, the use of different radiation techniques (3DCRT, IMRT, and VMAT) may have introduced significant biases, particularly with respect to the dose distribution to the target area, which in turn could have significantly impacted on the progression pattern.

In conclusion, this retrospective study suggests that decreasing the irradiation treatment volumes in mGBM does not significantly affect oncological outcomes. However, to validate these findings, it is essential to conduct prospective multicenter studies, which should include a detailed examination of dosimetric parameters and their implications for disease control.

## Statement of Ethics

This retrospective study was reviewed and approved by the Institutional Review Board of Siena University Hospital "Le Scotte" (No. 2023-01-001).

## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## Funding

None.

## Author Contributions

Conceptualization, FM, GLG, EC, MT, NDM, FG, AC, AP, MY, SA, LM, MAM, GM, PT; Investigation and methodology, FM, GLG, EC, MT, NDM, FG, AC, AP, MY, SA, LM; Writing of the original draft, MAM, GM, PT; Formal analysis, FM, GLG, EC, MT, NDM, FG, AC, AP, MY, SA, LM; Data curation, FM, GLG, EC, MT, NDM, FG, AC, AP, MY, SA, LM.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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