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Original Research

Association of pre-radiotherapy tumour burden and overall survival in newly diagnosed glioblastoma adjusted for *MGMT* promoter methylation status

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Importance of the study: In this retrospective study with clinical, genetic, and imaging data from two large randomised clinical trials, we found that the pre-radiotherapy volume of residual contrast-enhanced glioblastoma was associated with overall survival (OS) in patients receiving radio-/chemotherapy. While *MGMT* promoter methylation was clearly associated with better survival, both patients with *MGMT* promoter methylated and unmethylated tumours fared better with lower pre-treatment contrast-enhanced tumour volumes. These findings are in line with previous literature, showing a similar association between OS and residual tumour volume measured directly after surgery; our study adds to this evidence base by accounting for any changes occurring in the time period between resection and start of radiotherapy. Patients with the smallest *MGMT* promoter unmethylated CET volume (< 2 cm^3), however, still appeared to have worse survival than patients with the largest *MGMT* promoter methylated CET volume (< 15 cm^3). This underlines the strong prognostic value of *MGMT* promoter methylation in glioblastoma.

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KEYWORDS
Magnetic resonance imaging;
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Abstract ***Purpose:*** We retrospectively evaluated the association between postoperative pre-radiotherapy tumour burden and overall survival (OS) adjusted for the prognostic value of O^6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation in patients with newly diagnosed glioblastoma treated with radio-/chemotherapy with temozolomide.
Materials and methods: Patients were included from the CENTRIC (EORTC 26071-22072) and CORE trials if postoperative magnetic resonance imaging scans were available within a timeframe of up to 4 weeks before radiotherapy, including both pre- and post-contrast T1w images and at least one T2w sequence (T2w or T2w-FLAIR). Postoperative (residual) pre-radiotherapy contrast-enhanced tumour (CET) volumes and non-enhanced T2w abnormalities (NT2A) tissue volumes were obtained by three-dimensional segmentation. Cox proportional hazard models and Kaplan Meier estimates were used to assess the association of pre-radiotherapy CET/NT2A volume with OS adjusted for known prognostic factors (age, performance status, *MGMT* status).
Results: 408 tumour (of which 270 *MGMT* methylated) segmentations were included. Median OS in patients with *MGMT* methylated tumours was 117 weeks versus 61 weeks in *MGMT* unmethylated tumours ($p < 0.001$). When stratified for *MGMT* methylation status, higher CET volume (*HR 1.020; 95% confidence interval CI [1.013–1.027]; $p < 0.001$*) and older age (*HR 1.664; 95% CI [1.214–2.281]; $p = 0.002$*) *were* significantly associated with shorter OS while NT2A volume and performance status were not.
Conclusion: Pre-radiotherapy CET volume was strongly associated with OS in patients receiving radio-/chemotherapy for newly diagnosed glioblastoma stratified by *MGMT* promoter methylation status.

1. Introduction

Glioblastoma is the most common primary malignant brain tumour in adults, often with a poor prognosis despite maximal surgical resection followed by chemo- and radiation chemotherapy [1]. Contrast-enhanced magnetic resonance imaging (MRI) is the gold standard for glioblastoma treatment planning and surveillance [2,3].

Several studies [4,5] have investigated the prognostic value of residual contrast-enhanced tumour (CET) volume after surgery, suggesting that it is associated with survival in glioblastoma along with previously known prognostic factors. Additionally, 'supratotal' surgical resection which includes the non-enhancing tumour volume has been suggested because of the benefit on survival outcome in some previously published reports [6,7].

MGMT promoter methylation status is an important molecular marker in glioblastoma, since tumours with this methylation have better prognosis. Recently, several studies [8–10] have re-assessed the prognostic value of CET and non-enhanced T2 abnormalities (NT2A) residual volume, adjusting for the molecular profile in accordance to the 2016 World Health Organisation classification [11]. However, these studies investigated the prognostic associations of resection in the early postoperative stage, and did not take into consideration the tumour progression occurring in the period between resection and start of radiotherapy.

Thus, in this study, we aimed to assess the association between postoperative pre-radiotherapy tumour volume and overall survival (OS), adjusted for *MGMT* promoter methylation, in patients with newly diagnosed glioblastoma receiving radio-/chemotherapy.

2. Patients and methods

2.1. Patient inclusion criteria

We retrospectively assessed the data of 810 patients with newly diagnosed glioblastoma with respectively without *MGMT* methylation collected in the context of the companion CENTRIC EORTC 26071-22072 phase 3 and CORE phase 2 trials [12,13]. These trials aimed to explore the efficacy of cilengitide on OS, however, no effect was found. The pooled CENTRIC and CORE database contains the patients' clinical characteristics, that is, age (dichotomised as younger than versus older than or equal to 50 years), sex, Eastern Clinical Oncology Group performance score (ECOG score), OS; and tumour characteristics, namely centrally determined *MGMT* gene promoter methylation status and radiological assessments. MRI data were collected from participating sites and consisted of all trial scans from the moment of surgery. Preoperative imaging was not

collected. Patient characteristics and eligibility criteria for the respective trials have been reported elsewhere [12,13]; for inclusion of this imaging study the following additional criteria apply:

1. The availability of postoperative MRI scans within a time-frame of up to 4 weeks before the start of the radiotherapy (RTX) treatment (the postoperative MRI performed closest to start of RTX was used; the time between this MRI scan and the start of RTX is the RTX time interval);
2. The availability of the relevant MRI sequences for tumour segmentation: both pre- and post-contrast T1-weighted (T1w respectively post-contrast T1w) images and at least one T2-weighted sequence (T2w or T2w-FLAIR).

2.2. Tumour segmentation for volumetric measurements

The MRI scans were automatically sorted using DeepDicomSort [14] and manually checked to exclude scans with severe imaging artifacts.

The images were converted from DICOM to Nifty format (using dcm2niix [15] v1.0.20181125), co-registered to the post-contrast T1w scan (using Elastix [16,17] v4.8), skull-stripped (using HD-BET [18] git commit 41ebe0d) and corrected for MR bias field (using N4ITK [19] v1.6). HD-GLIO (https://github.com/NeuroAI-HD/HD-GLIO v1.5) was used for automated tumour segmentation if all four required MR sequences (T1w, T1w+c, T2w, T2w-FLAIR) were available. Two radiological manifestations were segmented:

1) CET as determined by the pre- and post-contrast T1w sequences;
2) Hyperintense areas on T2w/T2w-FLAIR images.

To obtain the volume of NT2A, known to be a combination of tumour infiltration and oedema, CET was subtracted from the total volume of T2w hyperintensity. All segmentations were assessed for quality and acceptance, and manually edited in case of poor segmentation using ITK-Snap [20]. In cases where automated segmentation was not possible, due to a missing T2w or T2w-FLAIR scan, segmentation was performed manually (N = 34).

2.3. Data analysis

All statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.), Medians and interquartile ranges were used to express the distribution of continuous data. Non-parametric tests were performed for non-normally distributed data, Mann-Whitney U tests were used for comparisons of clinical characteristics between the patients with versus without *MGMT* promoter methylation. A linear regression model was used to explore the association between CET and NT2A volumes after Log10 transformation. For the construction of Kaplan-Meier curves, CET volumes were divided into four categories (<2 cm^3, 2–5 cm^3, 5–15 cm^3, and >15 cm^3) in line with Wijnenga et al. [21]. NT2A volumes were divided into four categories according to first, second, and third quartiles. Additionally, the four-tier classification, taking both CET and non-contrast-enhancing tumour into account, for supramaximal resection as proposed by RANO*resect* was applied [22]. Log-rank tests and Kaplan Meier survival analyses were used to evaluate the association of CET and NT2A volumes and a combination thereof with OS; the derived *p*-values were Bonferroni corrected for multiple testing. Cox proportional hazard models were created directly in multivariate analyses due to sufficient number of events [23], investigating the association of the clinical characteristics and the continuous variable of CET/NT2A volumes with OS stratified by *MGMT* promoter methylation status. We also assessed the results of the model using the CET/NT2A volume categories, which are reported in the Supplementary file (Table 5). Since information on *IDH* mutation status was not routinely collected in the trials but has a known prognostic impact [24], all analyses were repeated in sensitivity analyses including only patients with confirmed *IDH* wild-type glioblastoma. The significance level was set at 5%.

3. Results

3.1. Patient characteristics

From the 810 patients in the combined CENTRIC and CORE database, 408 met all the inclusion criteria for this analysis (Fig. 1). Patient characteristics are described in Table 1. Median follow-up period from time of randomisation until last follow-up or death was up to 190 weeks during the CENTRIC and CORE trials with a median OS of 96 weeks. Median OS was significantly different ($p < 0.001$) between patients with an *MGMT* promoter methylated tumour (117 weeks) versus patients with an *MGMT* promoter unmethylated tumour (61 weeks). The majority of patients were 50 years or older (74.5%) and male (53.7%). These characteristics in addition to CET and NT2A volumes, and the median time interval between the MRI scan and the start of RTX were not significantly different between the patients with versus without *MGMT* promoter methylation. ECOG performance score was found to be significantly different ($p < 0.001$): patients with *MGMT* promoter methylated glioblastoma more often had an ECOG score of 0 (i.e. better performance). The *IDH* mutational status was known in 195 patients (48%), the vast majority having *IDH* wild-type glioblastoma (n = 184; 94%).

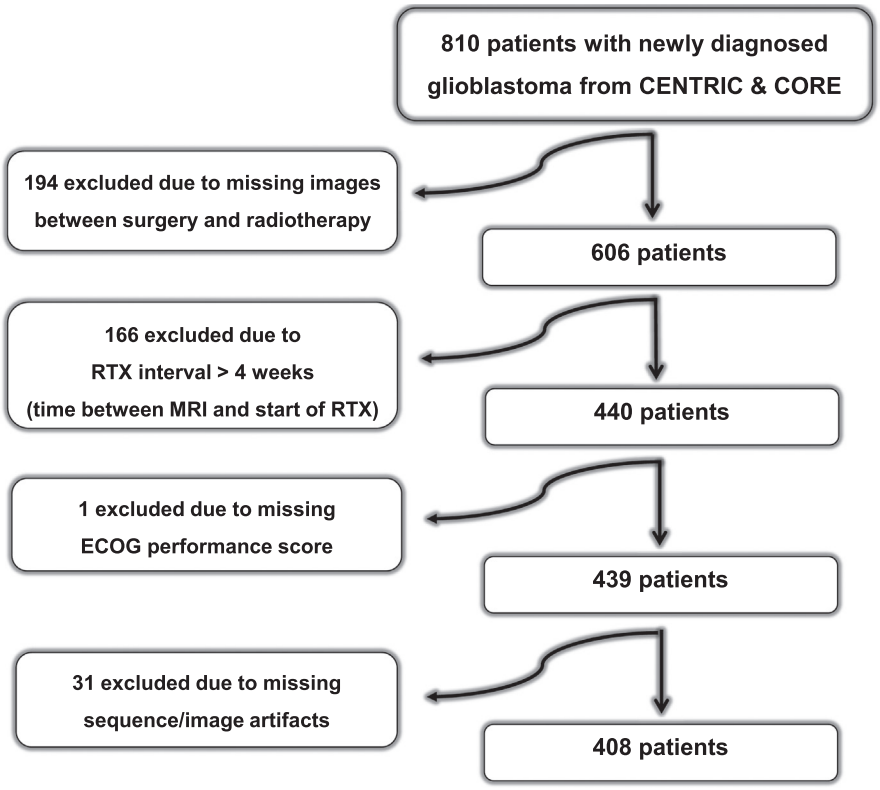

Fig. 1. Flow chart of patient inclusion. RTX, postoperative magnetic resonance imaging to start of radiotherapy time interval.

3.2. Association between CET and NT2A volumes

The correlation between the CET and NT2A volumes had a small magnitude (Spearman's rho = 0.311; $p < 0.001$). A 10% increase of CET volume was associated with an 1.8% increase of NT2A ($p < 0.001$; 95% confidence interval (CI) [0.124–0.255]) (Supplementary Fig. 1).

3.3. OS in relation to MGMT promoter methylation status

Both in patients with *MGMT* promoter methylated and unmethylated glioblastoma, there was an inverse relationship between CET volumes and OS (Figs. 2 and 3, Table 2). In patients with *MGMT* promoter unmethylated

Table 1
Patient characteristics.

Variables	All patients		*MGMT* promoter status		*p*-value*
	N = 408 (%)		Methylated N = 270 (66.2%)	Unmethylated N = 138 (33.8%)	Mann-Whitney U
Median OS (weeks) [IQR]		95.7 [87.2–104.2]	116.8 [97.1–136.6]	61.1 [55.8–66.4]	**<0.001****
Age	< 50 years	104 (25.5%)	61 (22.6%)	43 (31.2%)	0.061
Sex	Male	219 (53.7%)	140 (51.9%)	79 (57.2%)	0.302
ECOG performance score***	Score 0	215 (52.7%)	158 (58.5%)	57 (41.3%)	**<0.001**
Median RTX time interval (d) [IQR]		13.0 [8.0–18.0]	12.5 [7.0–18.2]	13.0 [9.7–17.0]	0.912
Median CET volume (cm^3) [IQR]		5.3 [1.6–15.3]	4.9 [1.5–14.7]	6.5 [1.6–16.6]	0.240
Median NT2A volume (cm^3) [IQR]		19.6 [8.7–43.1]	18.9 [8.7–40.9]	20.9 [9.5–46.5]	0.230

ECOG, Eastern Cooperative Oncology Group; RTX, postoperative magnetic resonance imaging to start of radiotherapy time interval; CET, contrast-enhanced tumour; NT2A, non-enhanced T2w abnormalities; IQR, interquartile range; OS, overall survival.
* Log rank comparison.
** Only patients with scores 0 and 1; no patients with ECOG score 2.
*** The significane level for p-value is set at 0.05.

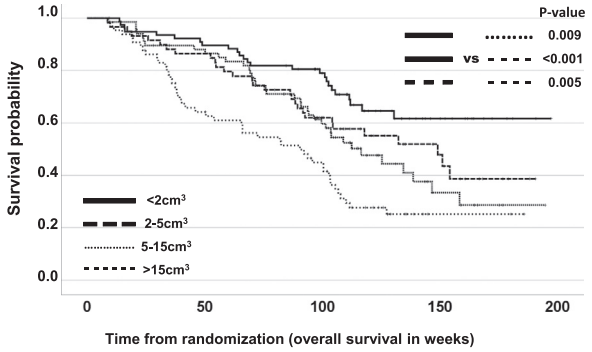

Fig. 2. Kaplan Meier survival curve of patients with *MGMT* promoter methylated glioblastoma for different contrast-enhanced tumour volume categories.

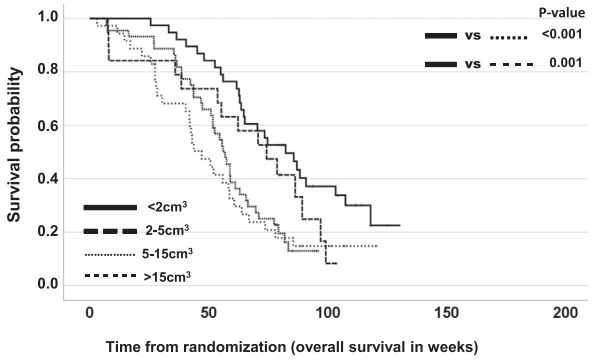

Fig. 3. Kaplan Meier survival curve of patients with *MGMT* promoter unmethylated glioblastoma for different contrast-enhanced tumour volume categories.

tumours, the difference in OS was significant in patients with CET volumes $< 2\,cm^3$ compared to patients with CET volumes $> 5\,cm^3$ and $> 15\,cm^3$ (82 weeks versus 56 weeks and 47 weeks, respectively), while in patients with *MGMT* promoter methylated tumours this difference was significant between all CET volume categories except for patients with CET volumes of 2–5 cm^3 versus any CET volumes $< 15\,cm^3$ and patients with CET volumes $> 15\,cm^3$ versus 5–15 cm^3. Patients with the largest CET volume ($> 15\,cm^3$) of *MGMT* promoter methylated tumour still appeared to have better OS compared to patients with the smallest CET volumes ($< 2\,cm^3$) of *MGMT* promoter unmethylated tumour, with a median OS of 90 weeks compared to 82 weeks, respectively (Table 2).

The volume of NT2A did not reveal a significant correlation in OS, irrespective of the *MGMT* promoter methylation status (Supplementary Table 1).

The combined CET/NT2A classification showed no significant difference in OS in patients with *MGMT* promoter unmethylated tumours whereas in patients with *MGMT* promoter methylated tumours, the difference in OS was significant ($p < 0.001$) in patients with maximal CET resection (Class 2) compared to patients with submaximal CET resection (Class 3) (Supplementary Table 2; Supplementary Figs. 2, 3).

3.4. Cox proportional hazard analysis

CET volume (in cm^3) showed a highly significant association with OS with a hazard ratio (HR) of 1.020 (95% CI [1.013–1.027]; $p < 0.001$) in addition to age which was also significantly associated with OS (HR 1.664 for >= 50 versus < 50; 95% CI *[1.214–2.281]; p = 0.002). NT2A volume, sex, ECOG score, and RTX interval were not significantly associated with OS* (Table 3)

3.5. Sensitivity analysis

Sensitivity analyses performed in patients with confirmed *IDH* wild-type glioblastoma only (N = 184) yielded similar results to the main analysis (Supplementary Tables 3, 4).

Table 2
Median overall survival (OS, in weeks) and log rank comparison (Bonferroni corrected for multiple testing) between contrast-enhanced tumour volume categories.

MGMT promoter status	Categories	Patients N = 408	OS in weeks	$< 2\,cm^3$ *p*-value*	$2–5\,cm^3$ *p*-value*	$5–15\,cm^3$ *p*-value*	$> 15\,cm^3$ *p*-value*
Unmethylated	$< 2\,cm^3$	39	82	-	0.132	**< 0.001**	**0.001**
	$2–5\,cm^3$	19	74	0.132	-	0.109	0.189
	$5–15\,cm^3$	44	56	**< 0.001**	0.109	-	0.483
	$> 15\,cm^3$	36	47	**0.001**	0.189	0.483	-
	Overall	138	61				
Methylated	$< 2\,cm^3$	77	**	-	0.066	**0.009**	**< 0.001**
	$2–5\,cm^3$	59	149	0.066	-	0.454	**0.005**
	$5–15\,cm^3$	68	116	**0.009**	0.454	-	0.018
	$> 15\,cm^3$	66	90	**< 0.001**	**0.005**	0.018	-
	Overall	270	117				

OS, overall survival.
* The significance level for the Bonferroni adjusted *p*-value is set at **0.012.**
** Median survival was not reached in this patient group, with 67% of patients still alive after the follow-up period.

Table 3
Multivariate Cox regression model associating CET and NT2A volumes with OS stratified by *MGMT* promoter methylation status.

Variables	Hazard ratio [95% CI]	*p*-value*
CET volume (cm^3)	**1.020 [1.013–1.027]**	**< 0.001**
NT2A volume (cm^3)	0.999 [0.995–1.003]	0.542
Age (> versus < = 50 years)	**1.664 [1.214–2.281]**	**0.002**
Sex (female versus male)	1.076 [0.830–1.394]	0.580
ECOG score (score 1 versus score 0)	0.964 [0.745–1.246]	0.777
RTX-interval (d)	0.999 [0.980–1.018]	0.902

CET, contrast-enhanced tumour; NT2A, non-enhanced T2w abnormalities; ECOG, Eastern Cooperative Oncology Group; RTX, postoperative magnetic resonance imaging to start of radiotherapy time interval; OS, overall survival; CI, confidence interval.
* The significance level for *p*-value is set at 0.05.

4. Discussion

In this retrospective study with clinical, genetic, and imaging data from two large randomised clinical trials, we found that postoperative pre-radiotherapy CET volume was strongly associated with OS in patients receiving radio-/chemotherapy and that both patients with *MGMT* promoter methylated and unmethylated tumours fared better the lower the postoperative volume (i.e. lower postoperative pre-treatment CET volumes). Patients with the smallest *MGMT* promoter unmethylated CET volume (< 2 cm^3), however, still appeared to have worse survival than patients with the largest *MGMT* promoter methylated CET volume (> 15 cm^3).

MGMT promoter methylation has been advanced as an important predictive biomarker in neuro-oncology because of the benefit on survival derived from temozolomide in newly diagnosed glioblastoma as observed by Hegi et al. [25]. There has since been a growing body of evidence showing the prognostic impact of the *MGMT* promoter gene on survival in patients with malignant glioma [26–28]. In Binabaj et al.'s meta-analysis *MGMT* promotor methylation was found to be significantly correlated with favourable outcome on OS. Within our cohort and consistent with the findings of preceding literature, we observed that *MGMT* methylation was associated with longer OS. Our results suggested that patients with minimal residual CET volume of *MGMT* promotor unmethylated tumour had almost the same, possibly even somewhat worse, survival as patients with the largest CET volume of *MGMT* promotor methylated tumour.

Due to the independent effect of *MGMT* methylation status on OS as demonstrated in our log-rank comparison analyses, we stratified our Cox model for *MGMT* promoter methylation status, and demonstrated that CET volume was a prognostic factor of OS while adjusting for previously known prognostic factors. Previous literature already clarified that post-surgical CET volume negatively impacts the survival outcome in glioblastoma [3,4]. Ellingson et al. showed that post-surgical CET volume significantly influenced survival in glioblastoma independently from clinical covariates and the type of therapy employed [4]. Their cohort represents the largest study to evaluate the association of CET volume with OS. However, this study has a limitation that the *MGMT* promotor methylation status was not known and thus not taken into consideration.

In contrast to our study, previous studies investigated the tumour burden utilising the postoperative MR images collected in the early stage after resection. The assessment of the tumour residual volume at this time point (directly post-surgical images) might influence the clinical outcome and misestimate the prognostic value, because it does not take into consideration tumour growth or tumour recurrence which may occur after surgery prior to the initiation of treatment [29,30]. In a small study, Yamashita et al. found that malignant gliomas can double in mass in around 15.0–21.1 d [30]. Pirzkall et al. found that as many as 53% of their study cohort showed a new contrast-enhanced lesion or increased volume [29]. The difference in tumour burden between the directly post-surgically acquired MRI and initiation of treatment can thus be substantial and is accounted for in our study by using the MRI scan most closely acquired prior to radiotherapy. It should be noted, however, that at this later time point after surgery, CET could be overestimated due to contrast uptake related to surgical scarring. At the same time, it is reasonable to assume that the surgical scar enhancement may be similar after resection of MGMT methylated and unmethylated tumours, thus not substantially affecting our findings.

There is a growing understanding of the prognostic importance of non-enhanced tissue abnormality in glioblastoma to optimise current treatment strategies and ultimately prolong survival [5–8,31,32]. Lasocki et al. reported that non-contrast enhanced lesions on T2w-FLAIR in peripherally located glioblastoma were associated with worse survival compared to those without this component [31]. Grabowski et al. demonstrated the predictive value of T2w/T2w-FLAIR residual volume on survival in both univariate and multivariate analysis [5]. In accordance to these findings, Kotrotsou et al. revealed that high postoperative residual non-enhanced tumour volume on T2w-FLAIR (> 70 cm^3) corresponded to a worse prognosis while patients with lower volume had a significant survival benefit (5.6 months) [7]. We found that CET was significantly correlated with the NT2A volume. However, we found that only CET volume and the combined CET/NT2A classification were significantly associated with OS, and not the NT2A volume by itself. This disparity between our results and the previous findings might be related to assessing NT2A volume just prior to initiating radiotherapy treatment while previous study

by Molinaro et al. [8] and Incekara et al. [9] evaluated the T2w/FLAIR abnormalities as an early postoperative resection percentage in comparison to the preoperative volume. At the later postoperative stage we assessed, some of the initially non-enhanced tumour tissue may have progressed to enhance. In addition, there is the inherent limitation in any volumetric assessment of the non-enhanced tumour on T2w/T2w-FLAIR given the difficulties to discriminate non-enhanced tumour from other entities causing hyperintense T2w-signal intensity, It is therefore not entirely surprising, albeit still of interest, that the entire residual T2w/T2w-FLAIR abnormality does not correlate with outcome. In our study, we didn't assess PFS, because of the difficulties with pseudoprogression after combined chemoradiation treatment. Especially because patients with MGMT methylated tumours might have a higher chance of pseudoprogression, looking at PFS might be misleading and we opted to only assess the association of CET volume with OS instead of PFS as a more robust outcome measure. Finally, it could be hypothesised that the small percentage of *IDH* mutated tumours could have influenced the results, as these tumours have proportionally larger areas of NT2A and are associated with better prognosis than *IDH* wild-type glioblastoma. However, our sensitivity analyses performed in patients with confirmed *IDH* wild-type glioblastoma, showing similar results, make this less likely.

Our study had some limitations. *IDH* mutational status was only known in a proportion of patients, due to the fact that *IDH* was not part of the diagnostic criteria for glioblastoma when the trials were performed. As mentioned above, this also resulted in a small percentage of *IDH-mutated* tumour in the study cohort, with different prognosis from what is now considered glioblastoma [33]. We addressed this issue by performing sensitivity analyses in patients with confirmed *IDH* wild-type tumour only, which yielded similar results to the main analysis.

A further limitation is the retrospective nature of the study, leading to inherent difficulties of including a homogenous cohort of patients controlling for all the prognostic factors. However, this study concerned data from two prospectively conducted clinical trials in which such prognostic factors were also important for the primary outcome. Also, the proportion of *MGMT-methylated* tumours was higher than expected in the glioblastoma population. This can be explained by the fact that we used data from previously conducted trials in which *MGMT* methylation status was the discriminator and main inclusion criterion for both studies. The groups were well-balanced in terms of age and sex, but a larger proportion of patients with *MGMT* promoter methylated tumours had a better performance status introducing some bias. Therefore, clinical characteristics were adjusted for in the survival analysis. However, this limitation is offset by the large size of the study population.

Finally, the MRI scan acquisition was heterogeneous due to the multi-centre nature of these trials, being performed before standardised imaging protocols were implemented. This concerned both the timing with respect to the surgery and radiotherapy, and the MRI acquisition. The latter was addressed by meticulously checking and correcting all tumour segmentations. The former raises the question whether tumour growth could have occurred between the surgery and the pre-radiotherapy scan. However, there was no difference between the patient groups in the time interval between the start of radiotherapy and the pre-treatment scan.

In conclusion, we found that lower pre-radiotherapy CET volume after surgery was associated with longer OS. While *MGMT* promoter methylation was clearly associated with better survival, both patients with *MGMT* promoter methylated and unmethylated glioblastoma fared better with lower pre-radiotherapy tumour volumes.

Ethics committee approval

Obtained as part of the original trials.

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CRediT authorship contribution statement

Ahmad Alafandi: Methodology, Formal analysis, Writing – original draft. **Marion Smits**: Conceptualisation, Methodology, Writing – original draft, Writing – review & editing, Supervision, Project administration. **K.A. van Garderen**: Software, Writing – review & editing. **S. Klein**: Software, Writing – review & editing. **S.R van der voort**: Software, Writing – review & editing. **D. Rizopoulos**: Formal analysis, Writing – review & editing. **L. Nabors**: Investigation, Writing – review & editing. **R. Stupp**: Investigation, Writing – review & editing. **M. Weller**: Investigation, Writing – review & editing. **T. Gorlia**: Investigation, Writing – review & editing. **J.-C. Tonn**: Investigation, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: A. Alafandi; K. van Garderen; S. Klein; S. van der Voort; D. Rizopoulos; L. Nabors; T. Gorlia: None. R. Stupp: RS has acted or is acting as a scientific advisor to the following companies, none of which is relevant to the current manuscript: Alpheus Medical, AstraZeneca, Boston Scientific,

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.04.021.

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