

Subtraction MRI-based residual tumor volumetry outperforms extent of resection and enhances radiologic–molecular prognostication in glioblastoma

Silvano Filice^{a, #, *}, Antonio Pavarani^{b, #}, Francesco Chizzolini^b, Maria Michiara^c, Pellegrino Crafa^d, Giacomo Bertolini^e

^a Medical Physics Unit, Azienda Ospedaliero-Universitaria of Parma, Parma, Italy

^b Neuroradiology Unit, Azienda Ospedaliero-Universitaria of Parma, Parma, Italy

^c Medical Oncology Unit, Azienda Ospedaliero-Universitaria of Parma, Parma, Italy

^d Department of Medicine and Surgery, University of Parma, Parma, Italy

^e Neurosurgery Unit, Azienda Ospedaliero-Universitaria of Parma, Parma, Italy

ARTICLE INFO

Keywords:

Glioblastoma
Residual Tumor Volume (RTV)
Extent of Resection (EOR)
Subtraction MRI
MGMT Promoter Methylation
Prognostic biomarkers

ABSTRACT

Purposes: Extent of resection (EOR) is a traditional prognostic indicator in glioblastoma (GB), yet evidence suggests that residual tumor volume (RTV) may provide superior predictive value. Accurate RTV quantification is challenging due to postoperative imaging artifacts. This study evaluated subtraction MRI-based RTV as a prognostic biomarker compared with EOR and examined its interaction with MGMT promoter methylation status (MGMT_ms).

Methods: We retrospectively analyzed 83 patients with IDH-wildtype GB who underwent maximal safe resection followed by radiochemotherapy. RTV was quantified on postoperative MRI using a standardized T1-weighted subtraction workflow minimizing artifactual enhancement. Prognostic performance of RTV and EOR was compared through multivariable Cox analysis adjusted for age, performance status, and MGMT_ms. Bootstrap validation and analyses of long-term survivors (overall survival [OS] ≥ 28 months) were performed.

Results: Interobserver agreement for RTV was excellent (ICC = 0.91). RTV and EOR were significant predictors of OS in separate multivariable models, but only RTV retained significance when modeled together. The RTV-based model demonstrated superior discrimination (C-index 0.77) compared with the EOR-based model (C-index 0.62). An RTV threshold of 1 cm³ stratified patients into distinct prognostic groups (median OS 24 vs. 14 months, $p < 0.001$). MGMT_ms conferred a substantial survival benefit, particularly in patients with RTV ≤ 1 cm³. Among long-term survivors no covariates retained significance.

Conclusions: Subtraction MRI-based RTV quantification is superior to EOR for survival prediction in GB. Combining RTV with MGMT_ms enhances prognostic stratification, although current models do not fully explain long-term survival, highlighting the need for radiogenomic approaches.

The extent of resection (EOR), traditionally defined as the percentage reduction of contrast-enhancing tumor volume post-surgery, has long served as a central prognostic indicator in newly diagnosed glioblastoma (GB) patients. However, emerging evidence demonstrates that percentage-based EOR alone may be insufficient—and in some cohorts, less reproducible—as a predictor of overall survival (OS) [1–3]. A pivotal study by Grabowski et al. [4] found that contrast-enhancing residual tumor volume (RTV) was a more significant prognostic factor

than EOR when assessed in multivariate models. Likewise, Xing et al. [5] showed in a large retrospective cohort ($n = 292$) that while both EOR and RTV correlate with survival in univariate analyses, only RTV remained independently prognostic in multivariable modeling.

In light of this accumulating evidence, the RANO-Resect Working Group recently advanced a consensus classification system [6] for surgical resection in IDH-wildtype GB. This system emphasizes absolute RTV thresholds rather than relative percentage resection and

* Corresponding author at: Medical Physics Unit, Azienda Ospedaliero-Universitaria di Parma, via Gramsci 14, Parma 43126, Italy.

E-mail address: sfilice@ao.pr.it (S. Filice).

Silvano Filice and Antonio Pavarani contributed equally to this work.

incorporates the non-contrast-enhancing (nCE) infiltrative tumor component, as visible on T2-FLAIR, to define “supramaximal resection.” This harmonized framework fosters consistency in surgical reporting and enhances comparability across multicenter datasets. Although mathematically linked, RTV and EOR represent fundamentally distinct prognostic constructs. EOR conflates the magnitude of resection with preoperative tumor burden, rendering it susceptible to variability in tumor segmentation—whereas absolute RTV provides a direct estimate of residual disease burden capable of driving early recurrence. *Frontiers in Oncology* recently published a multicenter nomogram validation study [7] demonstrating a continuous inverse relationship between RTV and OS, reinforcing RTV’s role as a robust, reproducible biomarker for survival modeling (C-index \approx 0.75–0.80).

Quantifying RTV accurately remains technically challenging due to confounding postoperative changes (e.g., blood products, surgical debris) that can mimic enhancement [8,9]. Contrast-enhanced T1-weighted subtraction imaging—achieved by voxel-wise subtraction of co-registered pre- and post-contrast T1-weighted volumes—effectively isolates true residual enhancement, reducing measurement variability. This method has been validated across large cohorts and trials, demonstrating its utility in refining postoperative RTV quantification [10].

In parallel, molecular biomarkers such as MGMT promoter methylation status (MGMT_ms) significantly influence chemosensitivity and prognosis in GB. Evidence suggests that survival thresholds for both EOR and RTV may differ according to MGMT_ms, positing that combining molecular insights with volumetric imaging could enhance individualized prognostic stratification (e.g., MGMT-methylated patients with RTV ≤ 1 cm³ achieving markedly better outcomes) [6,11].

Therefore, this study aims to:

1. Compare the prognostic performance of RTV versus EOR for overall survival in patients with newly diagnosed IDH-wildtype GB—leveraging prior evidence that RTV demonstrates superior predictive accuracy. In this respect, we mitigated measurement bias by employing a standardized T1-weighted subtraction workflow to quantify RTV, enhancing delineation of true residual enhancement.
2. Evaluate the interaction between RTV and MGMT_ms within the long-survivor subgroup, to assess whether an integrated radiologic–molecular model enhances prognostic accuracy and informs surgical planning.

Materials and methods

Patient characteristics

We retrospectively analyzed a consecutive series of 96 patients with newly diagnosed IDH-wildtype GB treated between 2016 and 2023, classified according to the 2021 WHO criteria, who underwent maximal safe resection followed by standard radiochemotherapy and adjuvant temozolomide. Thirteen patients were excluded according to predefined criteria, resulting in a final cohort of 83 patients. Inclusion criteria were: (1) age >18 years; (2) availability of preoperative MRI performed within 10 days before surgery; (3) availability of postoperative MRI performed within 36–48 hours after surgery; (4) availability of MGMT promoter methylation status. Exclusion criteria were: severe comorbidities, poor image quality, and biopsy-only cases (RANO Resect Class 4). Baseline demographic, clinical, molecular, and imaging characteristics of the study cohort are summarized in Table 1 and Fig. 1. Performance status (PS) was assessed using the ECOG scale. Overall survival was defined as the time from diagnosis to death; data for eight patients were censored at the last follow-up. The study was approved by the local Ethics Committee, and was conducted in accordance with the Declaration of Helsinki.

Table 1

Baseline demographic, clinical, molecular, and imaging characteristics of the study cohort. Data are presented as absolute numbers unless otherwise specified. Age is expressed as mean with standard deviation (SD); volumetric and survival data are reported as median with interquartile range (IQR). Residual tumor volume (RTV) was stratified by the 1 cm³ threshold and MGMT promoter methylation status. The MGMT methylation threshold for dichotomization was set at 20%. Long-term survivors were defined as patients with overall survival (OS) \geq 28 months.

Characteristic	Value
Patients (#)	
all	83
male	47
female	36
Age (years)	
Mean (SD)	59 (12)
≤ 60	43
> 60	40
Tumor focality	
unifocal	71
multifocal	12
MGMT methylation state (#)	
methylated	26
unmethylated	57
Residual Tumor Volume (#)	
≤ 1 cm ³	60
methylated	16
unmethylated	44
> 1 cm ³	23
methylated	10
unmethylated	13
Pre-operative Tumor Volume (cm ³)	
median	37
IQR	16
Extent of Resection (%)	
median	98.5
IQR	16
Overall survival (months)	
median	17
IQR	16
Long-term survival	
# of patients	20

Imaging protocol and RTV measurement

MRI examinations were acquired on a 3.0-Tesla scanner (Discovery MR750; GE Healthcare) using a 32-channel head coil. The protocol included high-resolution 2D T1-weighted fast spin-echo sequences obtained before and after intravenous administration of gadoterate meglumine (0.1 mmol/kg). Pre- and post-contrast acquisitions were performed with identical field-of-view, matrix and geometry to optimize image registration. To reduce partial-volume effects and image noise in volumetric measurements, the axial 2D T1-weighted sequence was acquired with an in-plane resolution of 0.9 × 0.8 mm and a slice thickness of 1.0 mm with no interslice gap.

Image analysis was conducted on a commercial clinical workstation (Advantage Windows, version 4.7; GE Healthcare). Subtraction images were generated automatically after spatial registration and intensity normalization of the pre- and post-contrast T1 datasets; subtraction was performed on a voxel-by-voxel basis to produce maps that selectively highlight contrast enhancement while reducing postoperative and susceptibility-related artefacts. Bright voxels on the subtraction maps were interpreted as representing true contrast enhancement.

Two experienced neuroradiologists independently delineated the residual enhancing tumor on the axial subtraction dataset by manual contouring the enhancing areas on every axial slice; care was taken to exclude vascular structures and non-tumoral enhancement (Fig. 2). The software automatically interpolated the 2D contours to produce a three-dimensional rendering of the residual tumor and calculated the RTV.

Preoperative tumor burden was measured on axial post-contrast 2D

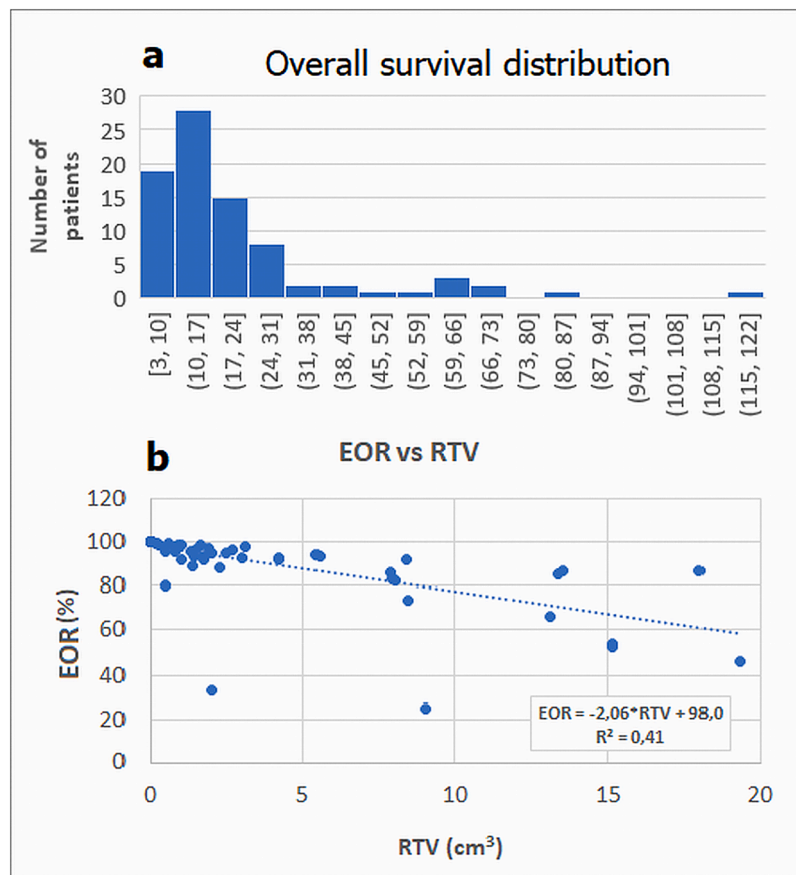


Fig. 1. a) Histogram showing the distribution of overall survival (OS), expressed in months, across the patient cohort. b) Scatter plot illustrating the relationship between residual tumor volume (RTV) and extent of resection (EOR). A strong negative correlation was observed between the two variables (Pearson correlation coefficient $r = -0.64$).

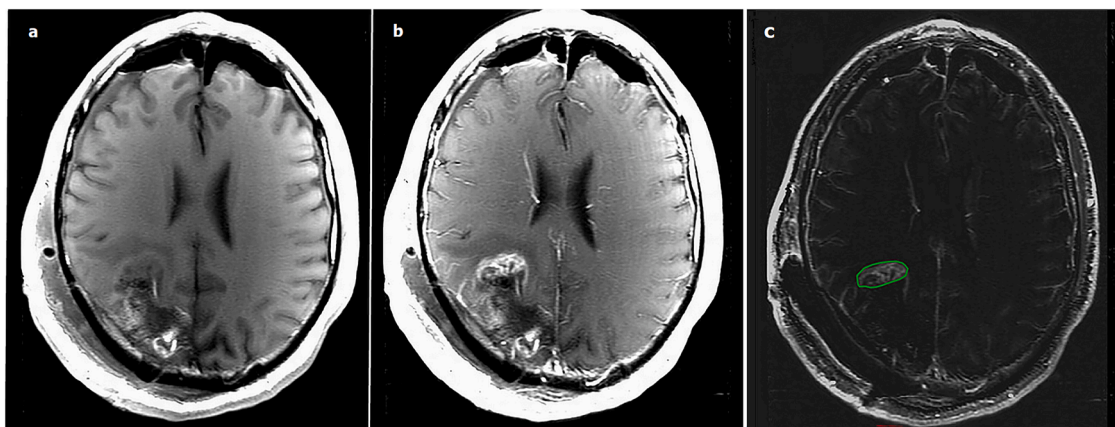


Fig. 2. Right posterior glioblastoma in a 62-year-old man. a) Postoperative high-resolution 2D T1-weighted FSE axial image. b) Postoperative high-resolution 2D contrast-enhanced T1-weighted FSE axial image. c) Subtraction image with contrast-enhancing area manually delineated from neuroradiologist (green line).

T1-weighted images by manual contouring of all enhancing tumor components, including necrotic regions; contours were reviewed to exclude vascular structures. The three-dimensional rendering of tumor and the corresponding pre-operative tumor volume (GTV) were calculated automatically by the workstation. The extent of resection (EOR) was expressed as a percentage and calculated as:

$$\frac{GTV - RTV}{GTV} \cdot 100$$

DNA samples

Genomic DNA was extracted from FFPE tissue sections using a MagCore kit and quantified with a Quantus fluorometer. Bisulfite-converted DNA was analyzed by pyrosequencing (PyroMark Q96 ID system) with the MGMT plus kit, covering 10 CpG sites in the MGMT promoter. For this study the methylation status was classified as methylated if the average methylation across sites was $\geq 20\%$.

Statistical analysis

- The statistical analyses were performed using SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA).
- Interobserver agreement for RTV quantification was assessed by calculating the Intraclass Correlation Coefficient (ICC) using a two-way random-effects model, single measurement, absolute-agreement definition. The ICC was interpreted as follows: > 0.90, excellent agreement; 0.75–0.90, good; 0.50–0.74, moderate; and < 0.50, poor agreement. For all subsequent analyses, the measurements from the more experienced observer were used to ensure

consistency and minimize potential variability in imaging assessment.

- The correlation between RTV and EOR was assessed using the Pearson correlation coefficient (r), with strength categorized as: |r| > 0.8, very strong; 0.6–0.8, strong; 0.4–0.59, moderate; 0.3–0.39, weak; and < 0.3, negligible.
- Univariate Cox proportional hazards models were used to investigate the association between OS and the following variables: RTV, EOR, MGMT_ms, GTV, gender, age, PS, and tumor focality (unifocal or multifocal). Variables with p < 0.10 in univariate analysis were considered eligible for inclusion in multivariable models.

Multivariable Cox Models

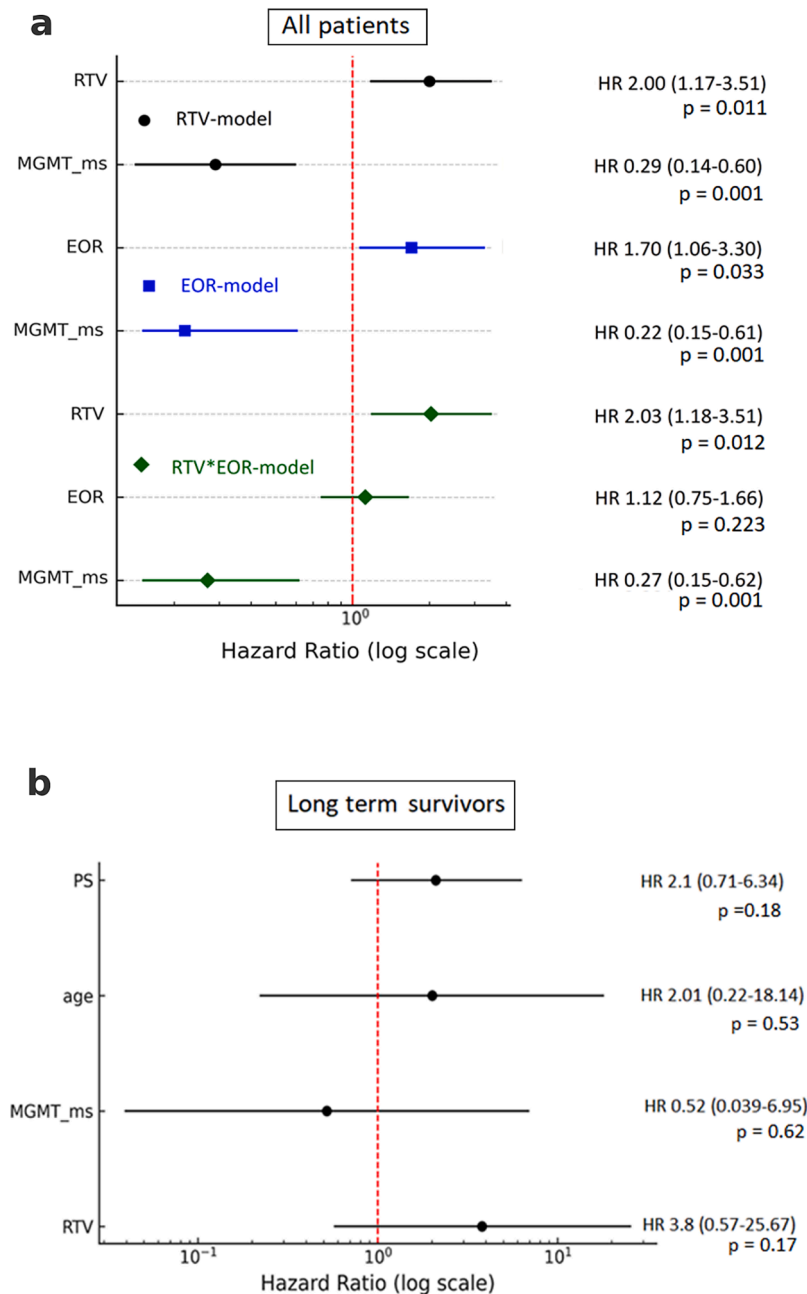


Fig. 3. Forest plot depicting hazard ratios (HR) and 95 % confidence intervals (CI) for key covariates across three multivariable Cox regression models. a) RTV-model (black circles) incorporates MGMT methylation status (MGMT_ms) alongside residual tumor volume (RTV), whereas EOR-model (blue squares) includes extent of resection (EOR) and MGMT_ms. RTV-EOR-model (green diamonds) includes RTV, EOR and MGMT_ms. b) Forest plot for long-term survival patients (OS ≥ 28 months): none of the tested variables retained significance in the multivariable regression model.

- Two separate multivariable Cox proportional hazards models were constructed to evaluate the prognostic impact of RTV and EOR on OS, each adjusted for the selected clinical and molecular covariates. This approach was chosen to minimize the effect of collinearity between RTV and EOR, thereby preserving model stability and interpretability. For clarity, we refer to the first model as the RTV-model and the second as the EOR-model. Additionally, a multivariable Cox regression model including both RTV and EOR (RTV*EOR-model) was performed to assess their independent prognostic contributions to OS. For each model, the concordance index (C-index) and the statistical significance of the overall model fit (likelihood ratio test) were calculated. The C-index was interpreted according to commonly used thresholds: ≈ 0.5 , no discrimination; 0.60–0.70, poor; 0.70–0.80, acceptable; 0.80–0.90, excellent; and > 0.90 , outstanding discrimination.
- To assess the robustness of the Cox regression results, bootstrap validation with 1000 resamples was performed for all three models.
- Further multivariable Cox analyses were conducted within the subgroup of long-term survivors, defined as patients with OS ≥ 28 months. This threshold was derived from the survival plot of the examined cohort (Fig. 1)
- Kaplan–Meier survival curves and log-rank tests were used to compare OS between groups defined by RTV using a threshold of 1 cm^3 . This cut-off, proposed by the RANO Resect Group, distinguishes the prognostic Class 2B group (maximal CE resection) from the Class 3 group (submaximal CE resection).
- All statistical tests were two-sided, and p-values < 0.05 were considered statistically significant.

Results

- Interobserver agreement for RTV quantification was excellent (ICC = 0.91).
- A strong negative correlation was observed between RTV and EOR ($r = -0.64$) (Fig. 1a).
- Univariate Cox regression analysis showed that RTV, EOR, MGMT_ms, age, and PS were all significant predictors of OS, whereas GTV and tumor focality were not.
- RTV-model: MGMT_ms (HR = 0.29; 95 % CI = 0.14–0.60; $p < 0.001$), RTV (HR = 2.0; 95 % CI = 1.17–3.51; $p = 0.011$). The model demonstrated a high overall fit (likelihood ratio test, $p < 0.0001$) with a C-index of 0.77 (95 % CI = 0.68–0.76) (Fig. 3a).
- EOR-model: MGMT_ms (HR = 0.22; 95 % CI = 0.15–0.61; $p < 0.0001$) and EOR (HR = 1.70; 95 % CI = 1.06–3.3; $p = 0.033$) remained independent predictors of OS. The model also showed strong overall fit ($p < 0.0001$) with a C-index of 0.62 (95 % CI = 0.55–0.71) (Fig. 3b).

- RTV*EOR-model: Only RTV retained statistical significance (HR = 2.03; 95 % CI = 1.18–3.51; $p = 0.0115$), while EOR did not ($p = 0.223$). The overall model fit remained high ($p < 0.0001$) with a C-index of 0.78 (95 % CI = 0.69–0.77) (Fig. 3c)
- Both performance status (PS) and age (dichotomized at 60 years) were statistically significant independent predictors of OS in all three multivariable models evaluated. The HR, 95 % CI, and p-values for these two variables were remarkably consistent across the different models. The estimates derived from the RTV-model presented as a representative example were: age (HR = 3.13; 95 % CI = 1.72–5.70; $p < 0.0002$), PS (HR = 1.35; 95 % CI = 1.14–1.60; $p < 0.0005$)
- Bootstrap validation (1,000 resamples) confirmed the stability of HRs and 95 % CIs for all significant covariates in the overall cohort, supporting the robustness of the multivariable models.
- Consistent with the RANO Resect Group findings, an RTV threshold of 1 cm^3 effectively discriminated prognostic groups (Fig. 4). Patients in Class 2B (RTV $\leq 1 \text{ cm}^3$) had a median OS of 24 months, compared to 14 months for Class 3 (RTV $> 1 \text{ cm}^3$). A significant interaction between RTV and MGMT methylation status was observed: in Class 2B, MGMT-methylated patients exhibited a markedly longer median OS (43.0 months) compared to unmethylated patients (22.0 months). In Class 3, the survival benefit persisted but was reduced (17.0 vs. 13.0 months).
- In the multivariable Cox analysis restricted to long-term survivors (OS ≥ 28 months), no covariates, including RTV and MGMT_ms, were significantly associated with OS. The overall model fit was low, with $p = 0.31$ and C-index of 0.53 (95 % CI = 0.05–0.88) (Fig. 3c)

Discussion

In this study we show that a standardized T1-weighted subtraction workflow enables precise, reproducible quantification of RTV on early postoperative MRI, with excellent inter-reader agreement (ICC = 0.91). Methodologically, subtraction mapping reduces the confounding effect of postoperative blood products and reactive enhancement by voxel-wise removal of the pre-contrast signal from the post-contrast acquisition, thereby enriching for true contrast uptake. Prior work has demonstrated that such subtraction-based maps improve delineation and volumetry of enhancing glioma components, supporting their use as a measurement backbone for postoperative assessments [11–14]. Importantly, in our cohort early postoperative MRI was consistently performed within a narrow time window (36–48 hours after surgery), minimizing confounding effects of very-early or delayed imaging [15].

Against this technical backdrop, our comparative modeling indicates that RTV outperforms EOR as a prognostic imaging biomarker. Although both indices associated with OS in multivariable Cox models, RTV retained significance when entered jointly with EOR, and the RTV-based

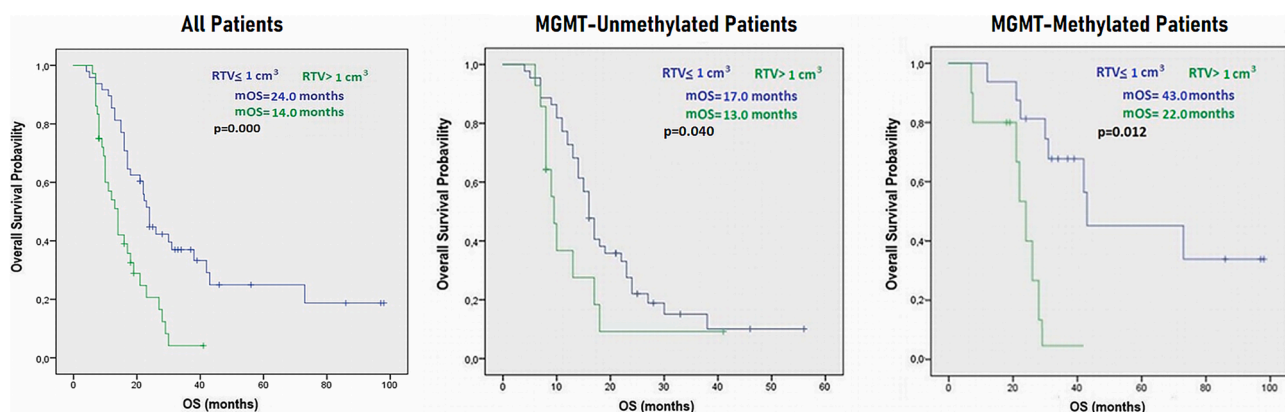


Fig. 4. Kaplan–Meier curves stratified by RTV and MGMT_ms. An RTV cut-off of 1 cm^3 distinguishes Class 2 from Class 3 prognostic groups according to RANO Resect classification 2023, with MGMT methylation consistently associated with longer survival. Log-rank p-values indicate statistical significance.

model yielded superior discriminative performance (higher C-index). These findings align with, and extend, the new RANO-Resect framework [6], which explicitly prioritizes absolute RTV over percentage EOR for postoperative classification in IDH-wildtype GB. In line with this framework, we specifically tested the robustness of our workflow against the 1 cm³ RTV boundary that separates RANO-Resect Class 2B (maximal CE resection) from Class 3 (submaximal CE resection), and we reproduced a step-change in median OS across these strata. By privileging absolute residual burden—rather than a percentage normalized to preoperative size—this approach mitigates EOR's dependence on baseline tumor volume and preoperative segmentation variability, and it more directly captures the substrate for early regrowth.

Our study further corroborates, in agreement with existing literature [16], the pivotal role of integrating molecular profiling into volumetric modeling, thereby reinforcing its prognostic and clinical significance in GB management. Consistent with contemporary evidence, MGMT promoter methylation demonstrated a stronger association with OS than any single imaging metric in our multivariable analyses, underscoring the primacy of molecular profiling for prognostication and treatment tailoring. At the same time, our data illustrate the complementary value of volumetry: the survival advantage of MGMT-methylated tumors was accentuated in patients achieving RTV \leq 1 cm³. These results are concordant with the ongoing shift toward radiologic–molecular risk stratification advocated by RANO-Resect and recent validation studies [17].

Our findings also speak to a persistent point of uncertainty in the field: the operational cut-off for MGMT methylation by pyrosequencing. While many centers dichotomize at ~9–10 %, multi-institutional series and methodologic reviews highlight that assay choice, CpG coverage, and analysis pipelines produce threshold variability and a “gray-zone” of intermediate methylation that warrants contextual interpretation. In our study, MGMT status was determined by pyrosequencing across 10 CpG sites using the MGMT methylation detection kit, and patients were dichotomized into methylated and unmethylated groups according to a predefined threshold [18–20], without adopting an intermediate category. These considerations reinforce the value of combining molecular status with quantitative imaging—rather than relying on either in isolation—when counseling patients and designing postoperative strategies.

A clinically relevant observation is that, within the long-survivor subgroup (OS \geq 28 months), none of the covariates examined—including RTV and MGMT_ms—retained a significant association with outcome. Although limited by sample size, this pattern suggests that exceptional survival in IDH-wildtype GB may be driven by unmeasured biological features (e.g., rarer molecular alterations, micro-environmental or immune factors) not captured by standard postoperative volumetry or binary MGMT classification [21,22]. This highlights a critical *limitation of current models* and outlines a research agenda centered on multi-omic profiling and radiogenomic integration in well-phenotyped long-survivor cohorts. This likely reflects the limited efficacy of current GB therapies, which constrains the predictive power of existing models and underscores the need for improved treatment approaches.

This retrospective, single-center study with limited statistical power and a reduced sample size, particularly relevant in the long-term survivor subgroup, did not fully account for GB molecular heterogeneity, which, according to the World Health Organization 2021 tumor Classification [23], includes prognostically relevant alterations such as TERT promoter mutations, CDKN2A/B homozygous deletions, and EGFR/PTEN pathway abnormalities, potentially confounding survival estimates, particularly in long-term GB survivors.

Even so, three practice-facing conclusions emerge:

Volumetric measurement: Routine adoption of subtraction-based RTV quantification is feasible and reproducible, providing a robust postoperative endpoint for clinical care and trials.

Prognostication: RTV should supersede percentage EOR when modeling survival and stratifying patients after surgery, in line with the RANO-Resect paradigm and its 1 cm³ decision boundary.

Integration: Prognostic accuracy improves when RTV is interpreted alongside MGMT_ms, yet current models underperform in long-term survivors, mandating next-generation, biology-informed predictors that integrate prognostically relevant molecular alterations in GB.

Collectively, these results strengthen the evidence base for RTV-first surgical reporting, advocate for radiologic–molecular risk integration, and delineate the space where existing predictors fail, namely, the tail of the survival curve, thereby motivating targeted discovery efforts in this distinct patient population.

CRediT authorship contribution statement

Silvano Filice: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Antonio Pavarani:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Conceptualization. **Francesco Chizzolini:** Visualization, Validation, Methodology, Conceptualization. **Maria Michiara:** Validation, Conceptualization. **Pellegrino Crafa:** Visualization, Validation. **Giacomo Bertolini:** Visualization, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Data availability

The authors do not have permission to share data.

References

- [1] P. Jagtiani, M. Karabacak, A. Carrasquilla, R. Yong, K. Margetis, Impact of Extent of Resection on Overall Survival in Glioblastomas: An Umbrella Review of Meta-Analyses, *Onco* (4) (2024) 359–368, <https://doi.org/10.3390/onco4040025>.
- [2] F. Revilla-Pacheco, P. Rodríguez-Salgado, M. Barrera-Ramírez, M.P. Morales-Ruiz, M. Loyo-Varela, J. Rubalcava-Ortega, T. Herrada-Pineda, Extent of resection and survival in patients with glioblastoma multiforme: Systematic review and meta-analysis, *Medicine* (Baltimore) 100 (25) (2021 Jun 25) e26432, <https://doi.org/10.1097/MD.00000000000026432>.
- [3] Kumar, Abhishek; Das, Kuntal K; Kanjilal, Soumen; Jain, Neeraj; Mishra, Prabhaker; Misra, Shagun; Bhaisora, Kamlesh S; Mehrotra, Anant; Jaiswal, Awadhesh K; Kumar, Raj. Potential and Pitfalls of Postoperative Volumetric Assessment of Extent of Resection in High-Grade Glioma in Resource-Constrained. [4] M.M. Grabowski, P.F. Recinos, A.S. Nowacki, J.L. Schroeder, L. Angelov, G. H. Barnett, MA. Vogelbaum, Residual tumor volume versus extent of resection: predictors of survival after surgery for glioblastoma, *J. Neurosurg.* 121 (5) (2014) 1115–1123, <https://doi.org/10.3171/2014.7.JNS132449>. NovEpub 2014 Sep 5. PMID: 25192475.
- [5] Y. Xing, X. Wang, Which Parameter Is More Important for the Prognosis of New-Onset Adult Glioblastoma: Residual Tumor Volume or Extent of Resection? *World Neurosurg.* 116 (2018) e444–e451, <https://doi.org/10.1016/j.wneu.2018.05.003>. AugEpub 2018 May 16. PMID: 29753893.
- [6] P. Karschnia, J.S. Young, A. Dono, L. Häni, T. Sciortino, F. Bruno, S.T. Juenger, N. Teske, et al., Prognostic validation of a new classification system for extent of resection in glioblastoma: A report of the RANO resect group, *Neuro Oncol.* 25 (5) (2023 May 4) 940–954, <https://doi.org/10.1093/neuonc/noac193>.
- [7] M. Skardelly, M. Kaltenstadler, F. Behling, I. Mäurer, J. Schittenhelm, B. Bender, F. Paulsen, et al., A Continuous Correlation Between Residual Tumor Volume and Survival Recommends Maximal Safe Resection in Glioblastoma Patients: A Nomogram for Clinical Decision Making and Reference for Non-Randomized Trials, *Front. Oncol.* 11 (2021 Dec 13) 748691, <https://doi.org/10.3389/fonc.2021.748691>. PMID: 34966669; PMCID: PMC8711700.

- [8] C.W. Wee, W. Sung, H.C. Kang, K.H. Cho, T.J. Han, B.K. Jeong, et al., Evaluation of variability in target volume delineation for newly diagnosed glioblastoma: a multi-institutional study from the Korean Radiation Oncology Group, *Radiat. Oncol.* 10 (2015 Jul 2) 137, <https://doi.org/10.1186/s13014-015-0439-z>.
- [9] R.Y. Huang, M.R. Neagu, D.A. Reardon, P.Y. Wen, Pitfalls in the neuroimaging of glioblastoma in the era of antiangiogenic and immuno/targeted therapy - detecting illusive disease, defining response, *Front. Neurol.* 6 (2015 Feb 23) 33, <https://doi.org/10.3389/fneur.2015.00033>.
- [10] B.M. Ellingson, L.E. Abrey, S.J. Nelson, T.J. Kaufmann, J. Garcia, O. Chinot, F. Saran, Nishikawa, et al., Validation of postoperative residual contrast-enhancing tumor volume as an independent prognostic factor for overall survival in newly diagnosed glioblastoma, *Neuro Oncol.* 20 (9) (2018 Aug 2) 1240–1250, <https://doi.org/10.1093/neuonc/nyy053>. PMID: 29660006; PMCID: PMC6071654.
- [11] B.M. Ellingson, D.T. Aftab, G.M. Schwab, C. Hessel, R.J. Harris, D.C. Woodworth, K. Leu, et al., Volumetric response quantified using T1 subtraction predicts long-term survival benefit from cabozantinib monotherapy in recurrent glioblastoma, *Neuro Oncol.* 20 (10) (2018 Sep 3) 1411–1418, <https://doi.org/10.1093/neuonc/nyy054>. PMID: 29660005; PMCID: PMC6120362.
- [12] B.M. Ellingson, H.J. Kim, D.C. Woodworth, W.B. Pope, J.N. Cloughesy, R.J. Harris, A. Lai, P.L. Nghiemphu, T.F. Cloughesy, Recurrent glioblastoma treated with bevacizumab: contrast-enhanced T1-weighted subtraction maps improve tumor delineation and aid prediction of survival in a multicenter clinical trial, *Radiology* 271 (1) (2014 Apr) 200–210, <https://doi.org/10.1148/radiol.13131305>.
- [13] C.W. Kanaly, D. Ding, A.I. Mehta, A.F. Waller, I. Crocker, A. Desjardins, D. A. Reardon, A.H. Friedman, D.D. Bigner, J.H. Sampson, A novel method for volumetric MRI response assessment of enhancing brain tumors, *PLoS One* 6 (1) (2011 Jan 26) e16031, <https://doi.org/10.1371/journal.pone.0016031>.
- [14] P.L. Kubben, A.A. Postma, A.G. Kessels, J.J. van Overbeeke, H. van Santbrink, Intraobserver and interobserver agreement in volumetric assessment of glioblastoma multiforme resection, *Neurosurgery* 67 (5) (2010 Nov) 1329–1334, <https://doi.org/10.1227/NEU.0b013e3181efbb08>.
- [15] A. Garcia-Ruiz, P. Naval-Baudin, M. Ligeró, et al., Precise enhancement quantification in post-operative MRI as an indicator of residual tumor impact is associated with survival in patients with glioblastoma, *Sci. Rep.* 11 (2021) 695, <https://doi.org/10.1038/s41598-020-79829-3>.
- [16] N. Wijethilake, M. Islam, H. Ren, Radiogenomics model for overall survival prediction of glioblastoma, *Med. Biol. Eng. Comput.* 58 (8) (2020) 1767–1777, <https://doi.org/10.1007/s11517-020-02179-9>. AugEpub 2020 Jun 3. PMID: 32488372.
- [17] Line Sagerup Bjorland, Rupavathana Mahesparan, Øystein Fluge, Bjørnar Gilje, Kathinka Dæhli Kurz, Elisabeth Farbu, Impact of extent of resection on outcome from glioblastoma using the RANO resect group classification system: a retrospective, population-based cohort study, *Neuro-Oncol. Adv.* 5 (1) (January-December 2023) vdad126, <https://doi.org/10.1093/oaajnl/vdad126>.
- [18] C. Fanizzi, P. Bintintan-Socaciu, E. Pirola, G. Fiore, I. Carnicelli, L. Taricotti, A. Parlangei, et al., Optimal MGMT promoter methylation cut-off to predict better survival in glioblastoma patients undergoing gross-total resection, *J. Neurosurg. Sci.* (2025 May 12), <https://doi.org/10.23736/S0390-5616.25.06421-5>. Epub ahead of print. PMID: 40351039.
- [19] N. Nguyen, J. Redfield, M. Ballo, M. Michael, J. Sorenson, D. Dibaba, J. Wan, G. D. Ramos, M. Pandey, Identifying the optimal cutoff point for MGMT promoter methylation status in glioblastoma, *CNS Oncol.* 10 (3) (2021 Sep 1) CNS74, <https://doi.org/10.2217/cns-2021-0002>. Epub 2021 Sep 6. PMID: 34486380; PMCID: PMC8461752.
- [20] L. Gurrieri, E. De Carlo, L. Gerratana, G. De Maglio, M. Macerelli, F.E. Pisa, E. Masiero, et al., MGMT pyrosequencing-based cut-off methylation level and clinical outcome in patients with glioblastoma multiforme, *Future Oncol.* 14 (8) (2018 Apr) 699–707, <https://doi.org/10.2217/fon-2017-0437>. Epub 2018 Mar 9. PMID: 29521523.
- [21] N. Briceno, E. Vera, E. Komlodi-Pasztor, Z. Abdullaev, A. Choi, et al., MR. Long-term survivors of glioblastoma: Tumor molecular, clinical, and imaging findings, *Neurooncol. Adv.* 6 (1) (2024 Feb 8) vdae019, <https://doi.org/10.1093/oaajnl/vdae019>. PMID: 38420614; PMCID: PMC10901543.
- [22] C. Hertler, J. Felsberg, D. Gramatzki, E. Le Rhun, J. Clarke, R. Soffiatti, W. Wick, O. Chinot, et al., Long-term survival with IDH wildtype glioblastoma: first results from the ETERNITY Brain Tumor Funders' Collaborative Consortium (EORTC 1419), *Eur. J. Cancer* 189 (2023 Aug) 112913, <https://doi.org/10.1016/j.ejca.2023.05.002>. Epub 2023 May 8. PMID: 37277265.
- [23] D.N. Louis, A. Perry, P. Wesseling, D.J. Brat, I.A. Cree, D. Figarella-Branger, C. Hawkins, H.K. Ng, S.M. Pfister, G. Reifenberger, R. Soffiatti, A. von Deimling, D. W. Ellison, The 2021 WHO Classification of Tumors of the Central Nervous System: a summary, *Neuro Oncol.* 23 (8) (2021 Aug 2) 1231–1251, <https://doi.org/10.1093/neuonc/noab106>. PMID: 34185076; PMCID: PMC8328013.