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Impact of extent of resection on outcome from glioblastoma using the RANO resect group classification system: a retrospective, population-based cohort study

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Abstract

Background. Extent of resection (EOR) is associated with survival in glioblastoma. A standardized classification for EOR was lacking until a system was recently proposed by the response assessment in neuro-oncology (RANO) resect group. We aimed to assess EOR in an unselected glioblastoma cohort and use this classification system to evaluate the impact on survival in a real-world setting.

Methods. We retrospectively identified all patients with histologically confirmed glioblastoma in Western Norway between 1.1.2007 and 31.12.2014. Volumetric analyses were performed using a semi-automated method. EOR was categorized according to the recent classification system. Kaplan–Meier method and Cox proportional hazard ratios were applied for survival analyses.

Results. Among 235 included patients, biopsy (EOR class 4) was performed in 50 patients (21.3%), submaximal contrast enhancement (CE) resection (EOR class 3) in 66 patients (28.1%), and maximal CE resection (EOR class 2) in 119 patients (50.6%). Median survival was 6.2 months, 9.2 months, and 14.9 months, respectively. Within EOR class 2, 80 patients underwent complete CE resection (EOR class 2A) and had a median survival of 20.0 months, while 39 patients had a near-total CE resection, with ≤1 cm^3 CE residual volume (EOR class 2B), and a median survival of 11.1 months, $P < 0.001$. The 2-year survival rate in EOR class 2A was 40.0%, compared to 7.7% in EOR class 2B.

Conclusions. RANO resect group classification for the extent of resection reflected outcome from glioblastoma in a real-world setting. There was significantly superior survival after complete CE resection compared to near-total resection.

Key Points

- RANO classification for the extent of resection was highly prognostic in a real-world setting.
- Survival was significantly longer after complete resection compared to near-total resection.
- Evaluation of second-look surgery in glioblastoma should be explored.

Importance of the Study

The extent of resection (EOR) is an important prognostic factor in glioblastoma. A standardized classification for EOR has long been lacking. The response assessment in neuro-oncology (RANO) resects group has published a classification based on absolute residual tumor volumes. This classification has not been validated in other cohorts. Evaluation of unselected cohorts is important in order to assess the validity in a real-world setting. This study presents real-world data on the extent of resection, stratified by the recent RANO resect group classification, and its associations with survival. The RANO classification was highly prognostic in this unselected cohort. We observed significantly superior survival among patients having undergone complete CE (contrast enhancement) resection, compared to near-total CE resection, defined as residual CE tumor ≤1 cm^3. This supports an evaluation of the safety and benefit of second-look surgery in patients with unexpected and potential resectable residual tumors.

The standard of care in patients with glioblastoma is maximal safe resection followed by radiation therapy and concomitant and adjuvant temozolomide.[1] Incomplete resection or diagnostic biopsy are alternative approaches when gross total resection is not achievable. The prognosis from glioblastoma remains dismal with a median overall survival of less than 1 year.[2,3] Clinical studies have demonstrated a median survival of approximately 15–16 months in younger patients and less than 10 months in elderly patients (≥65–70 years) eligible for postoperative chemoradiotherapy.[4–6]

Extent of resection (EOR) is an important prognostic factor in glioblastoma, and was traditionally classified into gross total resection, incomplete resection and biopsy. Gross total resection is associated with survival benefits compared to incomplete resection and biopsy.[7,8] The survival benefit from incomplete resection has been questioned for a long time. While some studies have demonstrated a survival benefit from incomplete resection compared to a diagnostic biopsy, others have demonstrated modest or no benefit.[2,9–12] This may indicate that incomplete resection is a highly heterogeneous group, and the lack of a standardized classification system to categorize the extent of resection has long made it difficult to compare clinical studies and to determine prognosis based on EOR in clinical practice.

Many previous studies performing volumetric assessment and evaluation of the extent of resection have focused on the percentage of removed tumor volume.[13–17] A classification system that combines relative tumor reduction and absolute residual tumor volume has been proposed.[18] However, it has been presumed that the absolute residual volume may be a more important prognostic factor than the relative reduction of tumor volume.[19] In 2022, the response assessment in neuro-oncology (RANO) resect group published a revised classification system, based on the abovementioned system, but in contrast including absolute residual tumor volumes alone.[20] To the best of our knowledge, this recent classification has not been re-evaluated in subsequent studies or a real-world setting.

Clarifying the impact on survival from EOR in a real-world setting is important to facilitate clinical decision-making in patients where gross total resection is not feasible or achieved. In this study, we aimed to perform volumetric analyses and to apply the recent RANO resect group classification system for EOR on an unselected glioblastoma cohort, and to determine the impact of EOR on survival in a real-world setting.

Methods

Design and Sample

In this population-based retrospective cohort study, we identified all patients aged 18 years or older in the geographical region of Western Norway (Vestland and Rogaland counties) presenting with a histologically confirmed glioblastoma between 1.1.2007 and 31.12.2014. We excluded patients with previous low-grade glioma or synchronous cancer, and patients who were not residents in the region. All included patients fulfilled the diagnostic criteria for glioblastoma present at the time of diagnosis. Subsequently, we excluded patients with detected IDH mutation or 1p19q codeletion, as these are not classified as glioblastoma according to the current WHO 2021 classification.[21] Available preoperative T1-weighted contrast-enhanced MRI was mandatory for enrollment. For patients who had undergone resection, both preoperative and postoperative T1-weighted contrast-enhanced MRI were mandatory. Patients were retrospectively followed until death or until eight years after diagnosis.

Measures

We collected clinical characteristics from electronic patient records (Table 1). The comorbidity burden was retrospectively assessed using Charlson Comorbidity Score.[22] Performance status was not assessed by standardized tools (ECOG or KPS) in most patients, and therefore not included in the analyses. Severe gait dysfunction was defined as the inability to walk without support, and cognitive impairment as any cognitive symptom. Postoperative chemoradiotherapy was classified as Stupp protocol (here defined as radiation therapy 60 Gy in 2 Gy fractions, concomitant temozolomide (TMZ) in the entire radiation period, and the completion of at least 1 out of 6 planned TMZ monotherapy courses), less intensive chemoradiotherapy (all other regimens of radiation therapy and/or TMZ), or best supportive care.

Table 1. Clinical Characteristics of 235 Patients With Histologically Confirmed Glioblastoma in Western Norway Between 1.1.2007 and 31.12.2014

	n	(%)
Clinical Characteristics		
Age ≥ 70 years	57	(24.3%)
Sex (female)	100	(42.6%)
Charlson Comorbidity Score ≥ 7	14	(6.0%)
Cognitive impairment	110	(46.8%)
Severe gait dysfunction*	26	(11.1%)
Epilepsy	83	(35.3%)
Headache	113	(48.1%)
Paresis	72	(30.6%)
Dysphasia	53	(22.6%)
Multifocality	56	(23.8%)
Corpus callosum affection	53	(22.6%)
Main tumor location		
Frontal lobe	55	(23.4%)
Temporal lobe	64	(27.2%)
Parietal lobe	21	(8.9%)
Occipital lobe	6	(2.6%)
Overlapping	73	(31.1%)
Deep-seated†	16	(6.8%)
Surgery		
Biopsy	50	(21.3%)
Resection	185	(78.7%)
Postoperative treatment		
Chemoradiotherapy		
Stupp protocol‡	126	(53.6%)
Less intensive§	95	(40.4%)
None	14	(6.0%)
Radiation therapy		
Full-course (60 Gy in 2Gy/fx)	164	(69.8%)
Short-course‖	56	(23.8%)
None	15	(6.4%)
Temozolomide		
Concomitant and adjuvant	132	(56.2%)
Concomitant or adjuvant	55	(23.4%)
None	48	(20.4%)

All variables are presented in absolute numbers and percentages (%).
*Severe gait dysfunction is defined as the inability to walk without support.
†Deep-seated is defined as tumor located mainly in deep structures including the thalamus, basal ganglia, internal capsule, splenium corpus callosum, mesencephalon, brain stem, and cerebellar vermis.
‡Stupp protocol is defined as radiation therapy 60 Gy in 2 Gy fractions with concomitant temozolomide during the entire radiation therapy period and fulfilled at least 1 of 6 planned temozolomide monotherapy courses.
§Less intensive chemoradiotherapy is defined as chemoradiotherapy otherwise.
‖Any regimen of hypofractionated radiation therapy. **Abbreviations:** fx = fraction.

Time from surgery to postoperative MRI, slice thickness, tumor location, and multifocality were noted. Multifocality was defined as 2 or more tumors unequivocally separated from each other, and satellite tumors located near the primary tumor were not interpreted as multifocality. Nonenhancing lesions separated from the primary tumor were considered of uncertain etiology and were not considered multifocal glioblastoma. Deep-seated tumor location was defined as tumor mainly located in the thalamus, basal ganglia, internal capsule, splenium corpus callosum, mesencephalon, cerebellar vermis, or brain stem.

Delineation and volumetric assessment were conducted using the semi-automated Smartbrush tool of the software Brainlab Elements V.3.0.0.92 (Brainlab AG, Munich, Germany).[23] Contrast-enhancing (CE) tumor and necrosis were delineated in the axial, sagittal, and coronal planes, and 3D volumes were calculated and measured in cubic centimeters (cm^3) in pre and postoperative MR images. Postoperative precontrast T1-weighted images were used to distinguish postoperative hemorrhage from contrast-enhancing residual tumor. The reduction of tumor volume (given as a percentage) was calculated as preoperative contrast-enhancing volume-postoperative contrast-enhancing volume/preoperative contrast-enhancing volume × 100. EOR was categorized according to the RANO resection group classification system.[20] Disease progression was defined as unequivocal clinical and/or radiological progression. Time to progression and death were calculated from the date of biopsy or resection.

Statistics

Statistical analyses were performed in IBM SPSS Statistics V. 29.0.0.0 (Chicago, Illinois, US). *P*-values < 0.05 were considered statistically significant. Categorical data were presented as absolute numbers and percentages, and groups were compared by chi-square test or Fisher's exact test, as appropriate. In order to compare our results with previously published data, continuous data were presented as both median (IQR) and median (range), as well as mean (±SEM). Non-normally distributed data were compared by nonparametric tests (Mann–Whitney *U* test for 2 groups and Kruskal–Wallis test for more than 2 groups). Kaplan–Meier method and the log-rank test were applied for survival analyses. Unadjusted and adjusted Cox proportional hazards models were used for further survival analyses.

Ethics

The study was approved by the Regional Committees for Medical and Health Research Ethics (REK Vest 2014/1931). A written consent was obtained for patients who were alive at the time of inclusion, whereas a waiver of consent was approved for deceased patients.

Results

We identified 287 patients with histologically confirmed glioblastoma in the study period, and 266 patients eligible for further analyses. The inclusion and exclusion processes

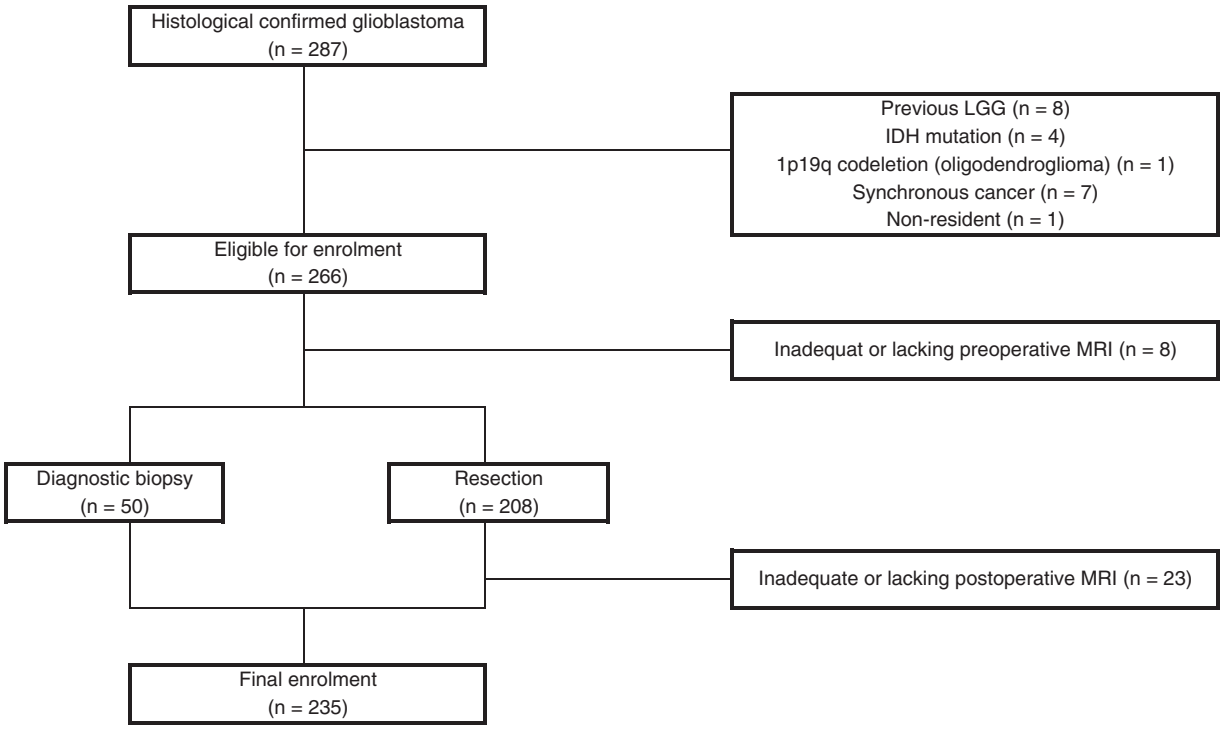

Figure 1. Enrollment of 235 patients with histologically confirmed glioblastoma in Western Norway between 1.1.2007 and 31.12.2014.

are presented in Figure 1. Preoperative MRI was lacking or inadequate for volumetric analyses in 8 patients. For patients having undergone resection, postoperative MRI was lacking or inadequate for volumetric analyses in 23 patients. Finally, 235 patients having undergone either gross total resection (n = 80), incomplete resection (n = 105) or diagnostic biopsy (n = 50) were enrolled. No patients were lost to follow-up.

Demographics and tumor characteristics are presented in Table 1. Median (range) age in the total cohort was 62.6 (25.4–86.1) years, and 135 of 235 patients (57.4%) were male, corresponding to a male:female ratio of 1:0.74. Among patients aged <70 years, 35/178 (19.7%) had a biopsy only, compared to 15/57 patients (26.3%) aged 70 years or more.

Multifocality was seen in 56 of 235 patients (23.8%), and more frequently among patients who underwent biopsy (26 of 50 patients (52.0%)) compared to resection (30 of 185 patients (16.2%)), $P < 0.0001$. Likewise, deep-seated tumor location was more frequent in the biopsy group (8 of 50 patients (16.0%)) than in the resection group (8 of 188 patients (4.3%)), $P < 0.01$. Among 64 patients with tumor in the temporal lobe, 61 patients (95.3%) underwent a resection, whereas 3 patients (4.7%) had surgery restricted to a diagnostic biopsy. In contrast, among 16 patients with deep-seated tumor, 8 patients (50.0%) underwent resection, whereas 8 patients (50.0%) had a diagnostic biopsy only.

Radiation therapy and/or TMZ were given to 221 of 235 patients (94.0%). The remaining 14 patients (6.0%) were treated with best supportive care only, more frequently among patients who had undergone biopsy (eight of 50 patients (16.0%)) than resection (six of 185 patients (3.2%)), $P = 0.001$.

Volumetric Analyses

Mean (SD) slice thickness in preoperative MRI was 1.1 mm (0.55). Mean (SD) slice thickness in postoperative MRI was 1.1 mm (0.15). Mean (SD) time from resection to postoperative MRI was 1.2 days (0.77). Median (IQR) and mean (±SEM) preoperative CE tumor volume in the total cohort was 25.9 (10.5–52.3) cm^3 and 34.9 cm^3 (±2.0), respectively, and ranged from 0.4 to 139.6 cm^3. Median (IQR) postoperative CE tumor volume among the 185 patients who underwent resection was 0.2 cm^3 (0.0–2.3) and ranged from 0.0 to 52.1 cm^3. The mean (±SEM) postoperative CE volume among resection patients was 3.2 (±0.6).

Tumor volumes, the extent of resection and outcome in the different EOR groups according to RANO resect group classification, including subclassification into 2 A/B and 3 A/B, are outlined in Table 2. In the total cohort, 119 patients (50.6%) were identified as EOR class 2, 66 patients (28.1%) as EOR class 3, and 50 patients (21.3%) had undergone a diagnostic biopsy (EOR class 4). Supramarginal resection (EOR class 1) was not performed in any of the included patients.

Median (IQR) preoperative tumor volume was larger in EOR class 3 (50.5 cm^3 (28.5–69.3)) than in EOR class 4 (17.0 cm^3 (10.0–37.4)) and EOR class 2 (20.4 cm^3 (7.5–38.5)), $P < 0.001$. Preoperative and postoperative CE tumor volumes stratified according to EOR classes are visualized in Figure 2.

Table 2. Tumor Volumes and Outcome Stratified by RANO resect group categories for the Extent of Resection (Karschnia et al., 2022) in 235 Patients With histologically Confirmed Glioblastoma in Western Norway Between 1.1.2007 and 31.12.2014

RANO* Categories for the Extent of Resection						
	Class 1 Supramaximal CE Resection†	Class 2 Maximal CE Resection		Class 3 Submaximal CE Resection		Class 4 Biopsy
		Class 2A† (complete CE resection)	Class 2B (near -total CE resection)	Class 3A (subtotal CE resection)	Class 3B (partial CE resection)	
Definition	0 cm^3 CE + ≤5 cm^3 nonCE	0 cm^3 CE + >5 cm^3 nonCE	≤1 cm^3 CE	≤5 cm^3 CE	>5 cm^3 CE	No tumor volume reduction
	n = 0 (0%)	***n*** = 80 (34.0%)	***n*** = 39 (16.6%)	***n*** = 39 (16.6%)	***n*** = 27 (11.5%)	***n*** = 50 (21.3%)
		n = 119		*n* = 66		
Preoperative CE tumor volumes						
Median (IQR)	n/a	17.2 cm^3 (6.7–34.2)	25.9 cm^3 (10.5–57.9)	36.4 cm^3 (13.7–52.5)	65.9 cm^3 (50.8–95.4)	17.0 cm^3 (10.0–37.4)
Mean (±SEM)		24.4 cm^3 (2.7)	36.2 cm^3 (5.2)	38.0 cm^3 (4.1)	72.4 cm^3 (6.2)	27.9 cm^3 (4.1)
Median (IQR)	n/a	20.4 cm^3 (7.5–38.5)		50.5 cm^3 (28.5–69.3)		17.0 cm^3 (10.0–37.4)
Mean (±SEM)		28.3 cm^3 (2.5)		52.1 cm^3 (4.1)		27.9 cm^3 (4.1)
Postoperative CE tumor volumes						
Median (IQR)	n/a	n/a	0.3 cm^3 (0.2–0.6)	2.2 cm^3 (1.4–2.9)	13.1 cm^3 (8.3–28.6)	n/a
Mean (±SEM)			0.4 cm^3 (0.04)	2.2 cm^3 (0.1)	18.1 cm^3 (2.5)	
Median (IQR)	n/a	0.0 cm^3 (0.0–0.2)		3.0 cm^3 (2.1–9.5)		n/a
Mean (±SEM)		0.1 cm^3 (0.02)		8.8 cm^3 (1.4)		
EOR‡						
Median (IQR)	n/a	100% (100.0–100.0)	98.5% (96.6–99.5)	94.2% (84.5–96.4)	77.1% (61.9–87.9)	n/a
Mean (±SEM)		100% (0)	96.7% (0.9)	87.8% (2.2)	73.1% (3.4)	
		100% (99.5–100.0)		87.9% (76.1–95.7)		
		98.9% (0.3)		81.8% (2.1)		
Outcome						
PFS						
	n/a	10.2 months (8.2–12.1)	6.9 months (5.9–7.9)	5.2 months (3.6–6.9)	5.7 months (4.9–6.6)	4.6 months (3.2–6.0)
		8.6 months (7.0–10.3)		5.5 months (4.5–6.4)		
OS						
	n/a	20.0 months (16.5–23.5)	11.1 months (9.9–12.3)	9.8 months (7.1–12.5)	8.8 months (6.7–10.9)	6.2 months (3.3–9.2)
		15.3 months (12.1–18.5)		9.2 months (7.7–10.7)		

Abbreviations: RANO = response assessment in neuro-oncology; CE = contrast enhancement; nonCE = noncontrast enhancement; EOR = extent of resection; PFS = progression-free survival; OS = overall survival.

Frequencies are presented as absolute numbers and % of total. Tumor volumes presented as CE tumor volumes in cm^3, EOR in % of preoperative CE tumor volume, and PFS and OS as median survival in months (95%CI).

*Referrers to the RANO resect group, an international multicenter group from seven neuro-oncological centers in US and Europe.

†None of the patients in this cohort underwent supramaximal CE resection, therefore nonCE was not measured and all patients with complete CE resection were categorized as class 2, regardless of nonCE volume.

‡EOR defined as % of CE tumor resected (formula: (preoperative CE volume-postoperative CE volume)/preoperative CE volume) × 100.

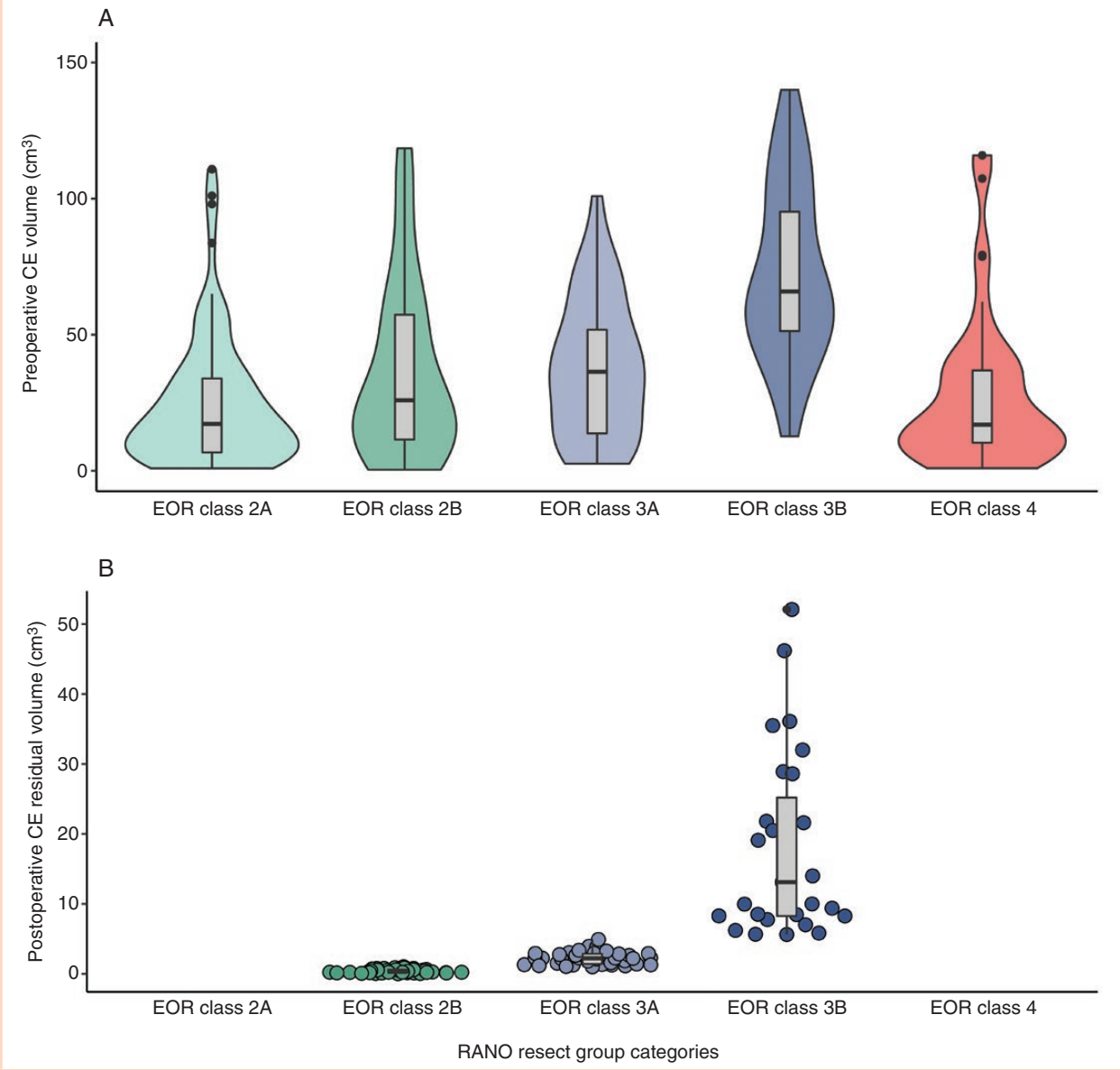

Figure 2. Preoperative contrast-enhancing (CE) tumor volumes (A) and postoperative CE residual tumor volumes (B), stratified by the extent of resection, in 235 patients with histologically confirmed glioblastoma between 1.1.2007 and 31.12.2014.

Outcome

Median progression-free survival in the total cohort was 6.7 months (95% CI 5.9–7.5), and median overall survival was 11.7 months (95% CI 10.4–13.0). Median survival was 6.2 months (95% CI 3.3–9.2) in the biopsy group and 13.1 months (95% CI 11.4–14.8) among patients who had undergone resection (EOR classes 2 and 3), $P = 0.001$. Among patients having undergone incomplete resection (EOR classes 2B, 3A and 3B), median survival was 10.7 months (95% CI 9.6–11.8). There was no statistically significant difference in median survival between biopsy and incomplete resection patients ($P = 0.27$). Progression-free survival and overall survival rates according to EOR groups are outlined in Table 2.

Patients in EOR class 2A had a median survival of 20.0 months (95% CI 16.5–23.5), whereas those in EOR class 2B had a median survival of 11.1 months (95% CI 9.9–12.3), $P < 0.001$. 2-year survival rate in class 2A was 40.0%, compared to 7.7% in class 2B. There was no difference in median survival between EOR classes 3A and 3B.

In the subgroup of 126 patients who were treated with full-course postoperative chemoradiotherapy according to the Stupp protocol, patients in EOR class 2A had a median survival of 24.6 months (95% CI 18.8–30.5), compared to 12.7 months (95% CI 10.2–15.2), 14.9 months (95% CI 2.0–27.7), 11.3 months (95% CI 7.7–14.9), and 12.0 months (95% CI 7.1–16.9), for those in EOR class 2B, 3A, 3B, and 4, <0.0001.

Median survival in elderly patients aged ≥70 years was 7.9 months (95%CI 5.3–10.5). Elderly patients ≥ 70 years in EOR classes 2, 3 and 4 had a median survival of 11.5 months (95% CI 8.1–14.9), 6.2 months (95% CI 5.1–7.3), and 3.5 months (95% CI 0.6–6.4), respectively ($P < 0.001$).

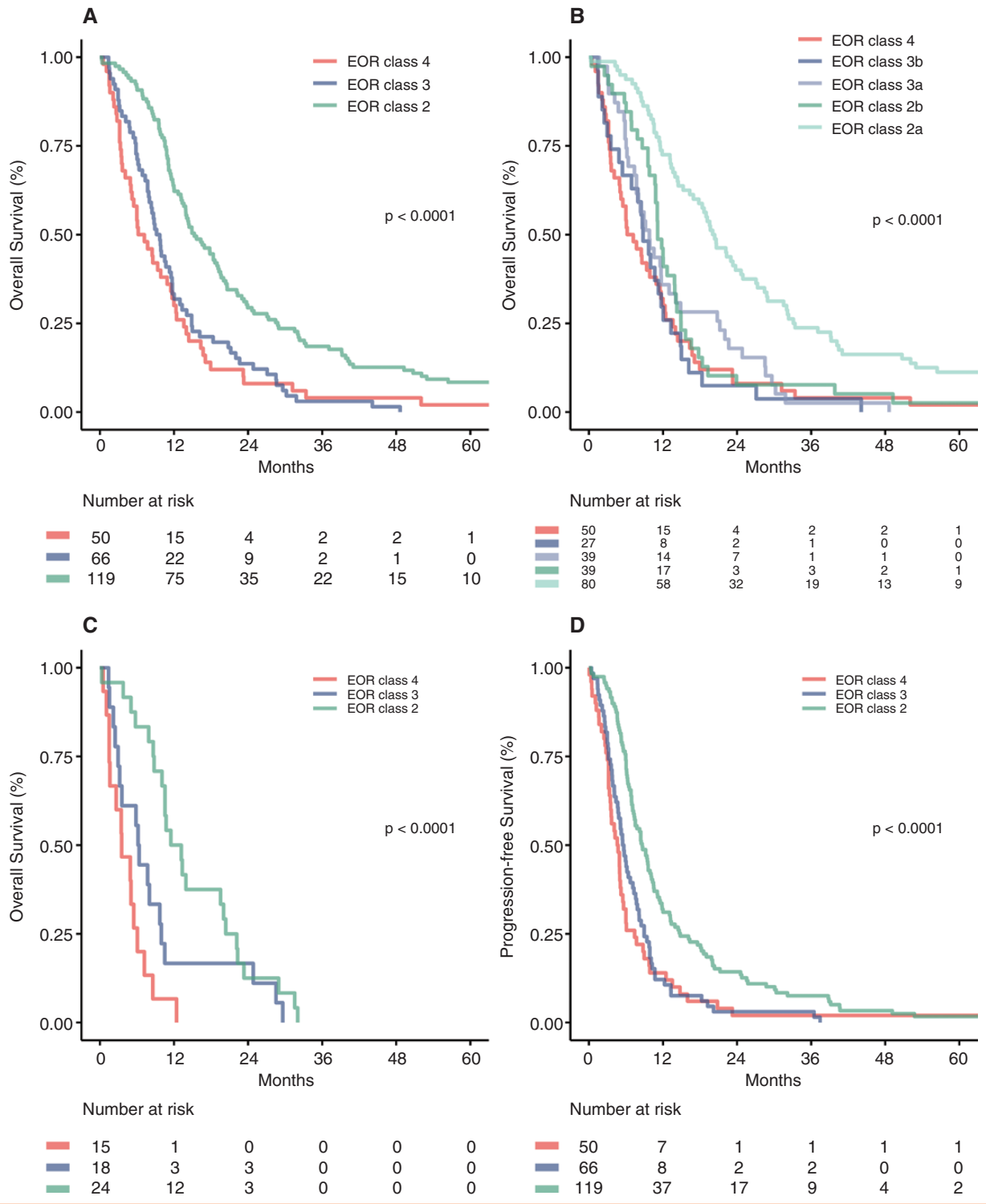

Figure 3. Survival probability in 235 patients with histologically confirmed glioblastoma in Western Norway between 1.1.2007 and 31.12.2014. Overall survival stratified by the extent of resection (EOR) classified according to the definitions by RANO resect group without (A) and with (B) EOR class 2A/B and 3A/B subgroups, overall survival among patients aged ≥70 years (C), and progression-free survival estimates in the total cohort (D).

One-year survival rates were 50.0%, 16.7%, and 6.7%, respectively. Kaplan–Meier curves on survival estimates are presented in Figure 3.

Univariate and multivariate Cox proportional hazard ratios are presented in Table 3. Higher age, multifocality, and chemoradiotherapy according to the EORTC

Table 3. Unadjusted and Adjusted Cox Proportional Hazard Ratio on Survival in 235 Patients in Western Norway With Histologically Confirmed Glioblastoma between 1.1.2007 and 31.12.2014

	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex (female)	0.91	0.70–1.18	0.47	1.07	0.81–1.41	0.65
Age (per year)	1.03	1.02–1.04	**<0.001**	1.03	1.02–1.04	**<0.001**
Deep-seated tumor*	1.53	0.92–2.55	0.10	1.37	0.79–2.39	0.27
Multifocality	1.77	1.30–2.42	**<0.001**	1.54	1.11–2.14	**0.01**
RT/TMZ (Stupp† vs all others)	0.44	0.34–0.58	**<0.001**	0.60	0.44–0.82	**0.001**
EOR (RANO resect group classification)‡						
Class 2A	Ref		Ref	Ref		Ref
Class 2B	1.16	0.72–1.86	0.55	2.33	1.56–3.47	**<0.001**
Class 3A	0.84	0.55–1.29	0.44	2.00	1.35–2.96	**0.001**
Class 3B	0.77	0.50–1.17	0.22	2.40	1.52–3.77	**<0.001**
Class 4 (biopsy)	0.40	0.28–0.57	**<0.001**	1.99	1.33–2.98	**0.001**

Abbreviations: HR = hazard ratio; CI = confidence interval; RT/TMZ = radiotherapy/temozolomide; EOR = extent of resection; RANO = response assessment in neuro-oncology; CE = contrast enhancement.
The extent of resection is classified according to the RANO resect group classification system (Karschnia et al., 2022). *P*-values < 0.05 are considered statistically significant and marked in bold.
*Deep-seated is defined as tumor located mainly in deep structures including the thalamus, basal ganglia, internal capsule, splenium corpus callosum, mesencephalon, brain stem, and cerebellar vermis.
†Here defined as RT 60 Gy in 2 Gy fraction and completed at least one out 6 planned TMZ courses.
‡EOR class 2A = complete CE resection; class 2B = near-total CE resection/≤1 cm^3 residual volume; class 3A = subtotal CE resection/≤5 cm^3 CE; class 3B = partial CE resection/>5 cm^3 CE; class 4 = biopsy/no reduction of tumor volume.

26981/22981 protocol were associated with inferior survival. EOR class 2A was associated with survival benefit in comparison with all other EOR classes, including EOR class 2B (HR 2.33 (95%CI 1.56–3.47)), $P < 0.001$.

Discussion

In this population-based retrospective cohort study on adult patients with histologically confirmed glioblastoma, we performed volumetric analyses and classified the extent of resection according to the recent classification system provided by the RANO resect group. To our knowledge, this is the first study to validate the prognostic impact of this classification, and the first study to perform survival analyses on EOR subclasses. We observed an increased longer overall survival along with higher EOR classes, both in the total cohort and among elderly patients. One-third of the patients in our cohort had a complete CE resection (EOR class 2A), associated with a favorable survival rate. It is important to emphasize the significantly superior survival among patients having undergone complete CE resection (EOR class 2A) compared to near-total CE resection with residual CE volume ≤ 1 cm^3 (EOR class 2B), with a median survival of 20 compared to 11 months.

Preoperative Tumor Volumes

Median and mean preoperative CE tumor volumes in our cohort were approximately 26 and 35 cm^3. This is comparable to results from previous studies performing volumetric assessments, where median and mean preoperative volumes ranged from 20–34 cm^3 to 29–38 cm^3, respectively.[13,19,20,24,25] Common to all these studies, including ours, is a wide range in preoperative tumor volumes, demonstrating the variability in presentation and volume needed to trigger healthcare contact in glioblastoma. The preoperative tumor volumes in EOR class 3 were larger than in EOR classes 2 and 4 (Figure 2). This may, as noted by Karschnia and colleagues, correlate with larger tumor volumes being more likely to involve eloquent areas and thus hampering maximal CE resection.[20]

Clinical Characteristics and Survival

The majority of previous volumetric studies have excluded patients with biopsy only, and the median age at the time of diagnosis was approximately 60 years.[16,19,24,25] In comparison, the median age in our cohort was higher (63 years), similar to comparable studies that included patients having undergone biopsy only.[11,15,20] Biopsy was performed in 21% of the patients in our cohort, in contrast to 7% RANO resect group cohorts presented by Karschnia and colleagues.[20] It is reasonable to assume that the higher frequency of poor prognosis patients in our cohort is due to the population-based study design and the real-world setting. This finding is also in accordance with a comparable study conducted by Incekara and colleagues, where 24% of the patients had a biopsy only.[11] Also, the occurrence of multifocal tumor was significantly higher in our cohort compared to the abovementioned study by Karschnia and

colleagues (24% vs 12%) while it was similar to a large study presented by Stark and colleagues.[20,26] We speculate that a lack of an established definition of multifocality in glioblastoma may explain these differences.

In our cohort, median overall survival was nearly 12 months, inferior to that observed in the in the RANO resect group cohort (17 months). Multiple factors may have contributed to this difference, including a higher frequency of multifocality, a three times higher frequency of biopsy only, and fewer patients receiving full-course chemoradiotherapy according to the EORTC 26981/22981 protocol (approximately 54% vs 80%).[27] It is reasonable to assume that patients with the most severe clinical presentations may be underrepresented in cohorts from tertiary referral centers. In addition, none of the patients in our cohort had a supramarginal resection, which is associated with favorable survival in young patients.[17]

The median survival rates observed in our study for patients who underwent biopsy and resection were 6.2 and 13.1 months, respectively. These findings align with the results of a prospective study conducted by Hrabalek and colleagues, where patients with tumors located in eloquent areas had a median overall survival of 3.5 months after biopsy, compared to 12.2 months for resection patients.[15] Furthermore, our results are consistent with previous volumetric studies that exclusively included resection patients, reporting median survival ranging from 12.2 to 13.4 months.[16,19,24,25] In line with several previous studies, we observed no significant difference in overall survival between biopsy and incomplete resection (EOR classes 2B, 3A, and 3B) patients.[9,10,12]

EOR Subclasses and Survival

The results from our study indicate that patients who achieved complete CE resection (EOR class 2A) had a median survival of 20 months, whereas those who underwent near-total CE resection (EOR class 2B) had a median survival of 11 months ($P < 0.001$). This finding is intriguing, particularly as the latter group included patients with residual tumor volumes of less than 1 cm^3. In contrast, the study from the RANO resect group reported only a slight difference in survival between EOR class 2A and 2B (median overall survival of 20 vs 17 months).[18,20] However, their analysis was based on a previous EOR classification system and a subgroup of patients who received full-course chemoradiotherapy. The contrasting results raise questions about the prognostic relevance of subclassifying EOR into 2A and 2B. While Karschnia and colleagues suggested that this subclassification may not have a prognostic significance, our data suggest the opposite. It is important to note that our study has limitations due to its retrospective design, and therefore, caution is needed in interpretation. Validation of these findings in future studies, preferably with a prospective approach, is necessary to confirm their validity and clinical implications.

Perioperative assessment of the extent of resection can be challenging as the perception of tumor removal may not always align with MRI findings, and residual CE tumor can be detected on postoperative MRI scans.[14] To improve the accuracy of EOR assessment, various technologies including intraoperative MRI, ultrasound, and navigation systems have been utilized. These technologies enhance the perioperative assessment of EOR by providing surgeons with valuable intraoperative imaging and guidance. In current clinical practice, very few patients undergo a second-look resection after unintended incomplete resection.[28] Small residual tumors may be considered adequately resected, and there is a lack of knowledge regarding safety and survival benefit from second-look surgery. A retrospective analysis of residual pediatric brain tumors concluded that second-look surgery was safe and led to increased tumor volume resection and a higher number of gross total resections, although long-term survival was not assessed.[29] A few small studies evaluated the results from second-look surgery in unintended or unexpected residual tumors in glioblastoma and found this strategy feasible and safe, however with limited data on long-term outcomes.[30,31] We propose that there may be a potential benefit from second-look surgery after unintended incomplete resections, including small residual tumors less than 1 cm^3, and this should be further investigated. Furthermore, these results emphasize the importance of intraoperative imaging in glioblastoma surgery.[32]

In line with previous studies, our data revealed no difference in survival between EOR classes 3A and 3B.[11,20] Our data demonstrated a trend towards longer survival after submaximal resection (EOR class 3) compared to diagnostic biopsy, however, this was not statistically significant (median overall survival 9.2 vs 6.2 months, $P = 0.57$). It is reasonable to assume that these survival rates may be biased by the selection of poor prognosis patients into the biopsy group.

Discussion of Methodology

Most previous studies conducting volumetric analyses of glioblastoma originated from tertiary referral centers and excluded patients with biopsy only and another poor prognosis patients.[13,14,16,19,24,25] Thus, it is important to evaluate the impact on survival from the extent of resection on an unselected glioblastoma cohort. According to the retrospective study design, the inclusion process was based on the diagnostic criteria present at the time of diagnosis. To achieve better alignment with the current WHO 2021 classification, all patients with known IDH mutation or 1p19q codeletion were excluded.

Inter- and intrarater reliability is a concern in volumetric analyses. As in previous volumetric studies, we applied a semi-automated volumetric assessment.[11,14,19,20,25] Semi-automated tools for volumetric assessments are considered reliable for the assessment of tumor volumes in glioma.[23,33] To counteract the methodical variabilities, all volumetric analyses were completed prior to survival analyses, all analyses were performed using the same software, and applied both pre and postcontrast T1 images to differentiate postoperative bleeding from CE residual tumor. Another methodological concern was the heterogeneity in MR protocols, slice thickness and imaging quality, related to the real-world study setting. We accepted this to obtain an unselected inclusion. Lastly, we did not include the assessment of nonenhancing T2 volumes, as none of

the included patients underwent supramarginal resection. However, parts of the nonenhancing lesions may have been removed together with the enhancing tumor in some cases, with a potential impact on survival.

Although time-consuming compared to two-dimensional assessments, we found volumetric analyses feasible, and considered the recent EOR classification system useful and applicable in the clinical setting. We expect that volumetric assessments will be increasingly available in both clinical studies and daily clinical practice, as they provide both prognostic information and may serve as a supplemental tool in clinical decision-making.

Strengths and Limitations

We consider the population-based study design and the real-world setting the most important strength of this study. Furthermore, only 1 patient was excluded due to lack of informed consent, and all patients were retrospectively followed for 8 years or until death, with none lost to follow-up. The most important limitation of this study was the lack of molecular data, as these analyses were not standard procedures in the region within the study period. O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation status and IDH mutations are prognostic factors, and the lack of routinely analyzing IDH mutational status and 1p19q codeletion may present a risk of inclusion bias. However, analyses of IDH mutational status and 1p19q codeletion were performed in selected cases, ie, in young patients and patients with histologically and/or radiologically suspected low-grade glioma. We, therefore, assume the risk of incorrectly including patients with IDH mutated glioma or oligodendroglioma as low. Also, the lack of objective data on functional status was an important limitation. Lastly, the significant number of patients excluded due to lack of adequate MRI is explained by the real-world study design. The reasons were multiple and highly variable, and thus it is considered unlikely to have caused a systematic inclusion error.

Conclusion

To conclude, we consider volumetric assessments using a semi-automated tool useful and feasible. The RANO resect group classification system for the extent of resection in glioblastoma was highly prognostic in a real-world setting. In particular, there was a noticeable superiority in survival after complete CE resection (EOR class 2A) compared to near-total CE resection (EOR class 2B), with a median survival of 20 versus 11 months. This emphasizes the importance of intraoperative imaging and may indicate a possible gain from second-look surgery in patients with unintended, resectable residual tumors.

Keywords

3D volumetric imaging | extent of resection | glioblastoma | real-world data | residual tumor volume

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Conflict of interest statement

The authors have no relevant financial or nonfinancial interests to disclose.

Authorship statement

All authors contributed to the study conception and design. Material preparation and data collection were performed by LSB, RM, and KDK. Volumetric analyses were performed by LSB and KDK. Statistical analyses were performed by LSB. All authors participated in the interpretation of the results. The first draft of the manuscript was written by LSB, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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