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RESEARCH

Surgical treatment of recurrent glioblastoma: A multicenter perspective from the Italian society of neurosurgery (SINch®) and a systematic review

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Abstract

Given the lack of effective second-line oncotherapy, the role of reoperation and the optimal treatment strategy for recurrent glioblastoma (rGBM) remains controversial. For this reason, we conducted a multicenter retrospective study joined with a systematic literature review to investigate the role of reoperation in patients with rGBM, to identify key factors for the selection of patients that can benefit from reoperation. A retrospective analysis of 236 surgically treated patients with rGBM from 14 different neurosurgical centers between 2012 and 2019 was performed. In addition, a systematic review of the literature was conducted with 87 papers (72 retrospective and 15 prospective) included in the final analysis. In our multicenter cohort, variables significantly relating with a longer post-recurrence survival (PRS) were Karnofsky Performance Status (KPS) at recurrence ($p=0.001$), tumor volume at recurrence ($p=0.011$), absence of ependymal involvement at recurrence ($p=0.022$), MGMT methylation both at first ($p=0.024$) and second surgery ($p=0.030$), supramaximal contrast-enhancing (CE) resection (RANO Class 1) both at first ($p=0.010$) and second surgery ($p=0.002$). After a review of the literature, reoperation and a higher preoperative KPS at recurrence were considered statistically significant variables for improved OS in 46/68 studies (68%) and 47/60 studies (78%), respectively. Maximal CE resection at first and second surgery was associated with a longer OS in 37/51 (73%) and 23/34 (68%) studies, respectively. RANO Class 1 resection and a Karnofsky Performance Status ≥ 70 at recurrence appear to be key prdictors to improved post-recurrence survival and preserving quality of life in rGBM patients. Additional factors, including tumor volume at recurrence, ependymal involvement, and MGMT promoter methylation status, should be carefully integrated into the multidisciplinary assessment of suitability for reopration in rGBM patients.

Keywords Glioblastoma · Multicenter · Recurrence · Second surgery · Recurrent glioblastoma

Introduction

Glioblastoma (GBM) is the most aggressive and the most frequent primary brain tumor in adults, with a peak incidence between 50 and 70 years old [1, 2]. Median overall survival (OS) is approximately 15 months from diagnosis [3]. The current standard of care for this condition includes surgery followed by chemotherapy and radiotherapy [4, 5]. It has been demonstrated that an Extent of Resection (EOR) threshold of 98% corresponds to a OS benefit, which is directly proportional to the EOR, calculated on volumetric assessment of enhancing region [6]. The aim of surgery is to achieve

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maximal contrast-enhancing (CE) resection, defined as resection without visual residual enhancing tumor [7, 8], avoiding post-surgical deficits and worsening quality of life.

Currently, there is no agreement concerning the management of rGBM [9, 10]. However, evidence remains preliminary, highlighting the need for randomized trials to guide recurrence management. Surgical benefit is suggested, but patient selection remains critical [11–18], and molecular investigation on rGBM failed to achieve results useful for clinical practice [14, 15].

The landmark DIRECTOR trial [19] demonstrated that reoperation may confer a survival advantage in highly selected patients, however highlighting the absence of standardized volumetric criteria. More recent investigations, including the RANO-resect consortium analysis [20] and the GBM trial [21] have refined the concept of surgical reintervention by defining the prognostic relevance of residual enhancing volume thresholds. The most recent meta-analysis [22] further confirmed that reoperation should be considered only when a residual CE volume < 1 cm³ can be achieved, with a pooled HR = 0.54 (95% CI 0.39–0.73, $p = 0.04$).

Considering these developments, the present study from the Italian Society of Neurosurgery (SINch®) provides an updated multicenter analysis of surgically treated recurrent rGBM cases, integrating volumetric EOR metrics according to the RANO-resect framework and a systematic synthesis of the literature. In this paper, we conducted a multicenter study and a systematic review of the existing literature to investigate the role of reoperation in patients with rGBM, reporting OS and KPS together with clinical, radiological and histopathological features, to detect key factors that influence PRS in selected patients with rGBM.

Methods

Study population

A retrospective analysis was conducted on 236 patients with rGBM who underwent surgical reoperation across 14 neurosurgical centers between 2012 and 2019. Eligibility criteria included: (1) histologically confirmed glioblastoma, (2) recurrence defined as the appearance of a new or enlarging contrast-enhancing (CE) lesion on T1-weighted MRI following initial treatment, and (3) surgical reintervention at recurrence. Collected data comprised clinical, radiological and histopathological features at both surgical time points.

The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee. Written informed consent was obtained from all patients prior to surgery.

Volumetric analysis

Volumetric assessments were retrospectively performed on pre- and postoperative 3D T1-weighted contrast-enhanced MRI (spoiled gradient echo sequences) using manual segmentation techniques. All measurements were independently reviewed by two investigators (T.I. and P.P.P.), with discrepancies below 5% resolved by consensus. Recurrence was defined according to RANO 2.0 criteria as either: (1) the appearance of new measurable CE lesions outside the radiation field, or (2) a > 25% increase in CE tumor volume compared with postoperative baseline MRI. Cases of pseudoprogression were excluded following multidisciplinary neuroradiological review. Tumor volume was expressed in cm³ and EOR was calculated, based on RANO-resect recommendations [20], as follows:

- Class 1 resection: supramaximal CE resection (0 cm^3 CE tumor + ≤ 5 cm^3 non-CE tumor);
- Class 2 resection: maximal CE resection (0–1 cm^3 CE tumor ± > 5 cm^3 non-CE tumor);
- Class 3 resection: submaximal CE resection (> 1 cm^3 CE tumor).

Endpoints

The primary endpoint was post-recurrence survival (PRS), defined as the time from tumor recurrence or second surgery to death or last follow-up. Although radiological recurrence preceded reoperation, the surgical date was chosen as a standardized and clinically meaningful landmark, ensuring consistency across centers and minimizing variability related to imaging timing.

Overall survival (OS) was consistently defined as the time from initial diagnosis to death or last follow-up. A secondary endpoint assessing quality-adjusted survival, termed Positive Outcome (PO), was defined as survival of at least 6 months combined with a Karnofsky Performance Status (KPS) ≥ 70 at 90 days following the second surgery, in order to assess both survival benefit and functional outcome [23] A PRS ≥ 6 months has been used in recurrent glioblastoma literature as a marker of relevant therapeutic benefit, while a KPS ≥ 70 at 90 days reflects preserved functional independence and eligibility for further oncological treatments [24].

Literature review

Three different medical databases (PubMed, Ovid MEDLINE and Ovid EMBASE) were screened in order to conduct a systematic review of the literature, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA) [25], evaluating the

role of second surgery in patients with rGBM. Records were searched for pertinent studies from 1970 to June 2025. Were viewed all abstracts of English-language articles containing the following keywords alone or in "AND" and "OR" combinations: "glioblastoma," "recurrence", "recurrent glioblastoma", "rGBM", "surgery," "surgical treatment", "reoperation", "second surgery".

Inclusion criteria were the following: (1) English language, (2) case series reporting more than 5 patients, (3) studies reporting recurrence of histological diagnosis of GBM, with or without adjuvant therapies. For each study, we extracted the following data: country, study period, study design, number of patients, age and gender, number of MCER at first and second surgery, percentage of patients receiving adjuvant therapies according to the Stupp protocol after first surgery, survival after first and second surgery.

Statistical analysis

The database was formatted through the Microsoft-Excel® software and later imported from the IBM-SPSS® software ver. 28.0.1 (IBM SPSS Inc. Chicago, Illinois). The use of Stata® software ver. 17.0 (Stata Corporation, College Station, Texas) was also considered for comparisons or implementations of test output. Normality of the distributions was assessed using the Kolmogorov-Smirnov test. Categorical variables were presented as frequencies or percentages and compared with the use of the Chi-Square test and the Fisher's exact test, as appropriate. Associations of the crosstabs were verified using standardized adjusted residuals, while was calculated the OR for 2×2 tables. Continuous variables were presented as means ± SD (in case of a normal distribution), or medians and min/max (in case of a skewed distribution) and compared with the use of the Mann-Whitney and Kruskal-Wallis test, whereas correlations among variables were compared by the Spearman's rank correlation test. Analysis of covariance and univariate and multivariate logistic regressions were conducted to study the relationships among dependent and independent variables.

Subgroup analyses were performed across multiple clinical, treatment-related, radiological, and histopathological variables. To estimate the causal effect of RANO-resect classes on PRS while accounting for potential selection bias, propensity score matching (PSM) was applied [26]. The exposure variable was defined as a binary comparison between Class 1 resections at recurrence (rClass 1) versus Class 2 resection (rClasses 2) and Class 3 resection (rClass 3) combined at tumor recurrence, with PRS as the outcome. Propensity scores were calculated using a logistic regression model incorporating baseline covariates known to influence both surgical selection and survival, including age, sex, recurrent tumor volume, and pre-reoperation KPS. A 1:1 nearest-neighbor matching without replacement was performed using a caliper width of 0.2 standard deviations of the logit of the propensity score. Covariate balance was assessed before and after matching to ensure comparability between groups, and post-matching analyses were conducted to evaluate the association between rClass and PRS. A two-sided α level of 0.05 was used for all tests. Figure 1 illustrates the population subgroups in which the different analyses were performed, stratified according to the selected endpoints and the availability of data.

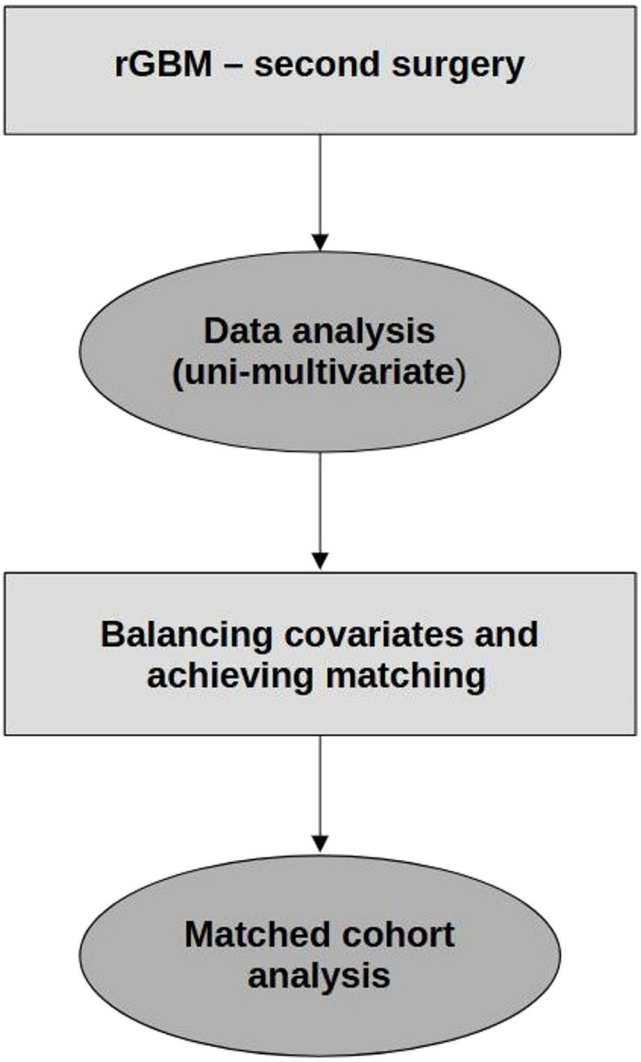

Fig. 1 All patients who underwent a second surgical intervention for rGBM were initially included. Following comprehensive data collection, uni- and multivariate analyses were performed to assess significant clinical and neuroradiological variables. Covariate balancing techniques were applied to refine the cohort, resulting in a final matched sample of patients. This subset was used for matched cohort analysis to evaluate treatment outcomes and prognostic factors with minimized selection bias

Results

Study population

Two hundred and thirty-six patients (65% males) with rGBM from 14 different neurosurgical Hospitals were surgically treated. The mean age was 57.3 years old (SD ± 11.8). After first surgery, 168 patients (71.2%) had Class 1 resection, whereas 50 patients (21.2%) had Class 2 resection and 18 (7.6%) had a Class 3 resection, respectively. Methylguanine-DNA methyltransferase (MGMT) was methylated in 79 (33.5%) patients at first surgery and in 54 patients (22.9%) at second surgery. A detailed summary is provided in Table 1.

One hundred ninety patients (80.5%) received conventional radiation therapy plus concomitant and adjuvant temozolomide chemotherapy after first surgery, according to the Stupp protocol [27]. The mean TTR from completion of initial irradiation was 14.3 months (range 0–101 months). One hundred one patients (42.8%) received other therapies at time of recurrence before reoperation.

One hundred thirty-six patients (57.6%) received adjuvant therapies after second surgery: 68 patients (28.8%) and 62 patients (26.3%) received temozolomide and fotemustine chemotherapy respectively, whereas 6 patients (2.5%) received radiation therapy.

Volumetric analysis

The median preoperative CE tumor volume at recurrence was 24.8 cm^3 (range 0.3–194.2), and the median postoperative residual volume was 0.7 cm^3 (range 0–6.8). Among the patients, 85 (36%) had tumors located in eloquent areas. In 50 patients (21.2%) the tumor involved the subventricular zone (SVZ) and in 34 (14.4%) the ependyma. The extent of

Table 1 Baseline characteristics of the multicenter SINch® cohort ($n = 236$)

Variable	Category/Description	*n* (%) or Mean ± SD
Demographics		
• Age (years)	Mean ± SD (range)	57.3 ± 11.8 (23–88)
• Sex	Male/Female	154 (65.3%)/82 (34.7%)
Clinical Features		
• Pre-recurrence KPS	Median (IQR)	82 (50–100)
• Time to recurrence (months)	Median (IQR)	14.3 (0–101)
• Neurological deficit before reoperation	Present	82 (34.7%)
• Seizures before reoperation	Yes	61 (25.8%)
Tumor Location		
• Lobar (frontal/parietal/temporal/occipital)		198 (83.9%)
• Deep/Thalamic/Insular/Periventricular		38 (16.1%)
• Dominant Hemisphere	Yes	112 (47.5%)
First surgery		
• Class1 resection	0 cm^3 CE tumor + ≤ 5 cm^3 non-CE tumor	168 (71.2%)
• Class 2 resection	0–1 cm^3 CE tumor ± > 5 cm^3 non-CE tumor	50 (21.2%)
• Class 3 resection	> 1 cm^3 CE tumor	18 (7.6%)
MGMT promoter methylation		
• First surgery	Methylated/Unmethylated/NA	79 (33.5%)/140 (59.3%)/17 (7.2%)
• Second surgery	Methylated/Unmethylated/NA	54 (22,9%)/162 (68,6%)/20 (8,5%)
Tumor Volume at recurrence		
• Preoperative CE tumor volume (cm^3)	Median (range)	24.8 (0.3–194.2)
• Postoperative residual CE volume (cm^3)	Median (range)	0.7 (0–6.8)
Treatment at Recurrence		
• Type of reoperation	Craniotomy with resection	236 (100%)
• Adjuvant therapy before reoperation	CT/RT/CT + RT	88 (37,3%)/7 (3%)/6 (2,5%)
• Adjuvant therapy after reoperation	CT/RT	130 (55,1%)/6 (2,5%)
Follow-Up and Outcomes		
• Median OS	Median (range)	28.8 (6–144)
• Median PRS (months)	Median (range)	11.2 (1–43)

Abbreviations: KPS = Karnofsky Performance Status; MGMT = O6-Methylguanine-DNA Methyltransferase; CE = Contrast-Enhancing; RT = Radiotherapy; CT = Chemotherapy

Table 2 Residual tumor volume after reoperation and PRS

Volumetric rClass (RANO-Resect Criteria)	*N* 197 (%)	Median PRS (months)	95% CI	HR (95% CI)	*p*-value
rClass 1 resection	94 (47.7%)	12.8	10.5–14.9	Reference	–
rClass 2 resection	47 (23.9%)	9.3	7.5–11.1	1.43 (1.02–2.00)	0.041
rClass 3 resection	56 (28.4%)	7.3	5.9–8.2	1.93 (1.31–2.86)	0.002

surgical resection, assessed in accordance with the RANO criteria (Class RANO), is summarized in Table 1 for the first surgical procedure and in Table 2 for the second surgical procedure (rClass RANO).

Survival analysis and outcome analysis

Median OS at diagnosis and following reoperation were 28.8 months (range 6–144) and 11.2 months (range 1–43) respectively. Variables significantly relating with a longer PRS were KPS at recurrence ($p=0.001$), tumor volume at recurrence ($p=0.011$), absence of ependymal involvement at recurrence ($p=0.022$), methylation of MGMT both at first ($p=0.024$) and second surgery ($p=0.030$), achievement of Class 1 resection both at first ($p=0.010$) and second surgery ($p=0.001$).

The median KPS at recurrence was 82 (range 50–100). Following reoperation, the median KPS was 78 (range 30 −100) and 74 (range 0–100) at 30 days and 90 days after surgery, respectively. rClass1 was significantly associated with favorable postoperative functional status, as indicated by a KPS≥70 at 90 days (OR=0.17, 95% CI; $p=0.00001$), and with prolonged PRS, defined as survival≥6 months (OR=0.28, 95% CI; $p=0.0004$).

Volumetric analysis was feasible in 197 of 236 patients (83,5%). The residual tumor volume was significantly associated with longer PRS (Table 2). Patients with rClass 1 resection had a median PRS of 12.8 months (range 10.5–14.9), compared with 7.3 months (range 5.9–8.2) for those with rClass 3 resection ($p=0.002$). Figure 2 illustrates the association between PRS and RANO-resect volumetric definitions. In multivariable Cox regression, KPS≥70 (HR 0.48, 95% CI 0.31–0.74, $p<0.001$) and rClass 1 resection (HR 0.52, 95% CI 0.33–0.81, $p=0.002$) remained independent predictors of improved PRS. A continuous correlation was observed between residual tumor volume and PRS ($r=0.61$, $p<0.001$).

Propensity score matching

Prior to matching, significant baseline imbalances were observed between rClass 1 and the control groups (rClasses 2 and 3). Specifically, rClass 1 patients presented with higher KPS scores, less frequent involvement of eloquent areas, and smaller recurrent tumor volumes, indicating a potential selection bias toward more favorable surgical candidates (Table 3).

PSM analysis was performed on the subset of patients with complete clinical and radiological data, enabling a 1:1 ratio matching ($n=130$). Incomplete molecular datasets prevented the incorporation of molecular markers as covariates in the PSM model.

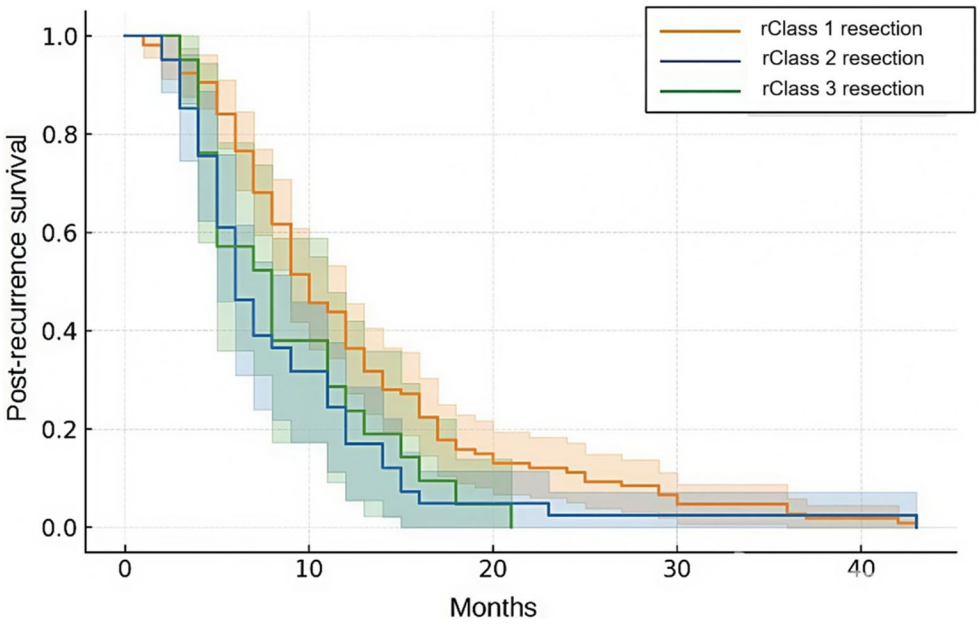

Fig. 2 Kaplan-Meier of PRS according to volumetric rClass (RANO-resect criteria). Data reported in Table 2

Table 3 Substantial imbalance in key covariates before PSM

Covariate	rClass 1 (*n*: 94)	rClass 2 + 3 (*n*: 103)	Pre-Matching Standardized Mean Difference (SMD)
Age (Mean ± SD)	57.0 ± 10.9	57.8 ± 10.6	0.07
Sex (Male) (*n*, %)	57 (60.6%)	72 (69.9%)	0.22
Eloquent Areas (*n*, %)	27 (28.7%)	44 (42.7%)	0.29
KPS pre-reop (Mean ± SD)	85.0 ± 12.3	75.3 ± 14.5	0.75
Recurrence tumor volume (Mean ± SD)	16.9 ± 17.5	30.7 ± 27.2	0.57

PSM effectively balanced all covariates, reducing SMDs below 0.1 (age 0.03, sex 0.08, eloquent areas 0.09, pre-reoperation KPS 0.05, recurrent tumor volume 0.07), indicating comparable groups. In the matched cohort, rClass 1 resection was associated with a significantly lower hazard of death compared to rClasses 2 and 3 (HR 0.65, 95% CI 0.45–0.94, $p = 0.02$), consistent with the difference in median survival observed in Table 2. PSM analysis demonstrated that rClass 1 resection was associated with a significant and independent improvement in PRS.

Literature review

A total of 2195 papers were identified after duplicates removal. After title and abstract analysis, 157 articles were identified for full-text analysis and 87 papers were included in this review [18, 19, 28–112]. PRISMA flow-chart is shown in Fig. 3. All studies analyzed are reported in detail in Table 4. Seventy-two studies (83%) were retrospective and 15 (17%) were prospective. A total of 16,761 patients were included, of whom 6380 (38%) underwent reoperation for tumor progression. 46/68 (68%) and 47/60 (78%) studies reported that reoperation and a higher preoperative KPS at recurrence, respectively, significantly improved OS. MCER at 1 st and 2nd surgery affects OS, as demonstrated by 37/51 (73%) and 23/34 (68%) studies, respectively. Overall, 76% of the studies were judged at moderate risk of bias, mainly due to heterogeneity in postoperative therapy and follow-up duration; 10% showed serious risk of bias for incomplete adjustment of confounders; and only 14% presented low risk of bias due to prospective design or predefined inclusion criteria (Table 5).

Discussion

Role of reoperation in recurrent glioblastoma: context and rationale

Given the consistently aggressive tumor biology and the absence of proven second-line systemic treatments, surgical management of rGBM continues to be one of the most debated topics in neuro-oncology [10, 11]. The survival benefit of reoperation has long been questioned due to high selection bias and heterogeneity in surgical endpoints across trials, even though it may offer cytoreduction, symptom alleviation, and renewed access to adjuvant treatments [17, 18]. Volumetric studies and the RANO-resect framework are two recent developments that have improved patient selection by showing that the degree of remaining contrast-enhancing tumor is a critical factor in PRS [20–22].

Within this evolving landscape, the present multicenter study aims to evaluate the role of surgery in rGBM as a targeted therapeutic strategy rather than a purely palliative intervention. By integrating standardized volumetric criteria, functional outcomes, and propensity score–adjusted analyses, our aim was to clarify whether maximal safe resection at recurrence confers an independent survival advantage and to identify clinical, radiological, and molecular factors that may guide patient selection for reoperation in contemporary practice.

Clinical and surgical treatment variables

A higher KPS at recurrence related to better PRS. Our literature review identified this variable as statistically significant for improved survival in the majority of studies (65%), consistent with the findings of our institutional case series analysis. However, many of the reported studies included both reoperated and non-reoperated patients, potentially leading to selection bias. We only included repeat resection (RR) candidates in our analysis, to avoid confounding factors which may overestimate the redo-surgery indication.

Age at recurrence was not associated with either KPS or post-recurrence survival in our cohort. While earlier reports suggested that younger age may favor repeat resection, increasing evidence indicates that functional status at recurrence is a stronger determinant of outcome than chronological age. In this context, patients with preserved performance status may benefit from reoperation regardless of age, including selected elderly individuals with KPS ≥ 70 [84, 90, 108, 112, 113].

Concerning the survival benefit of surgical resection in rGBM, the literature review suggests that RR significantly affects OS in 46/68 studies (68.5%). An improvement in OS associated with RR was observed in 11 of the 68

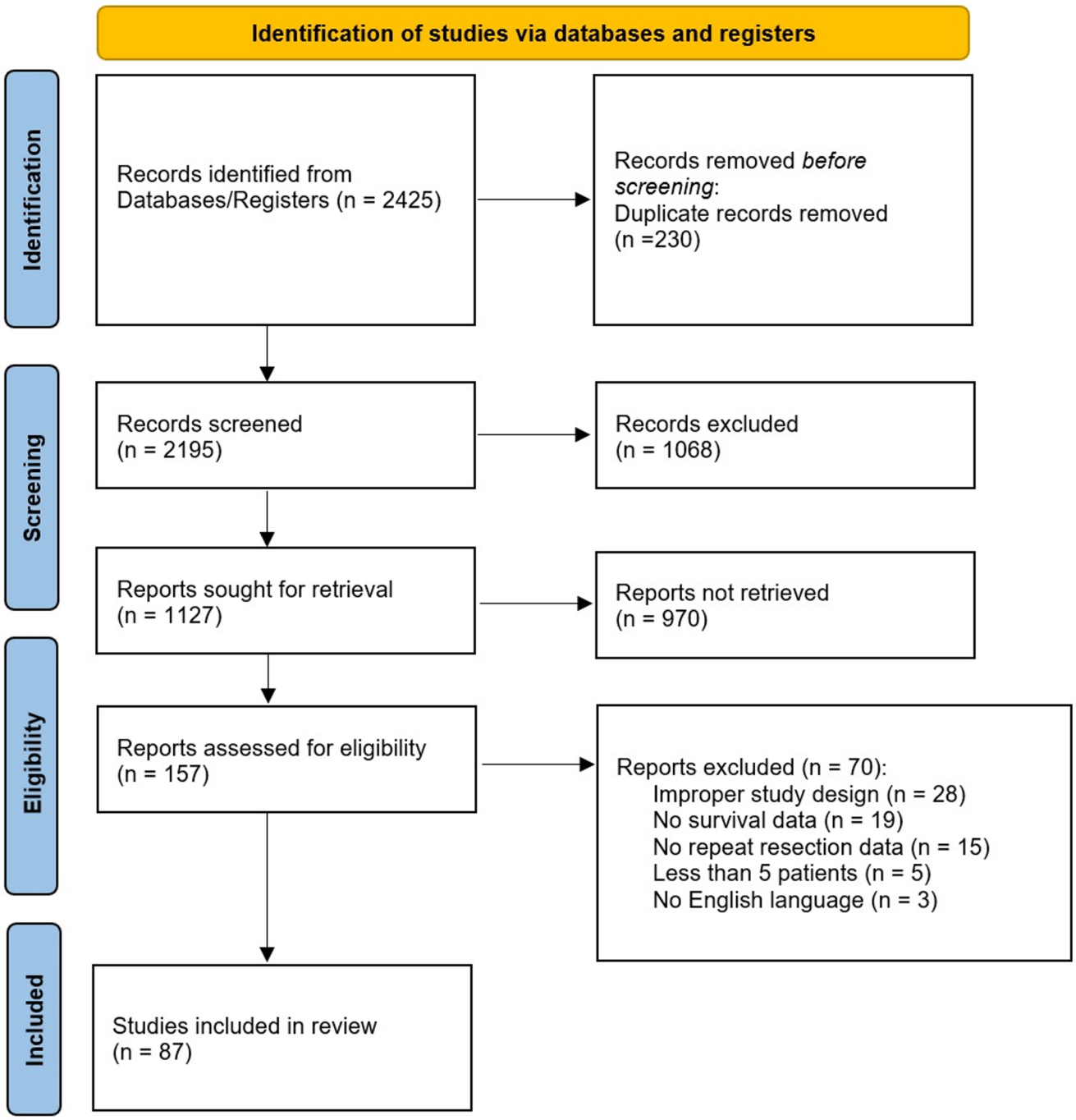

Fig. 3 PRISMA flow-diagram depicting the literature search process

studies (16.2%), although this finding was not confirmed by univariate or multivariate analyses. The extent of surgical resection was significantly associated with improved survival in 23/34 studies (67.6%), showed a non-significant association in one study, while no survival benefit was observed in 10/34 studies (29.4%).

In our multicenter cohort, even after accounting for major confounding factors, patients undergoing rClass 1 resection experienced a 35% lower risk of death (HR = 0.65, 95% CI 0.45–0.94; $p = 0.02$) compared with those receiving rClass 2 or 3 resections. This highlights that the extent of surgical resection is not only an independent prognostic factor for post-recurrence survival in rGBM patients, but also a clinically actionable determinant. These results suggest that, whenever feasible, achieving supramaximal CE resection should be considered a key therapeutic goal, rather than

Table 4 Summary table of the literature review

No.	Authors, Year	Study Period	Prospective or retrospective	Patients (*n*°)	Age (years; mean)	M: F	MCER at 1 st Surgery (*n*°)	Patients receiving STUPP (%)	Patients with RR, *n*° (%)	MCER at 2nd Surgery (*n*°)	RR Cohort OS from IS	Non-RR Cohort OS from IS	RR Cohort OS from RR	Non-RR Cohort OS from RR	EOR at 1 st Surgery Significant effect on Survival?	RR Significant effect on survival?	EOR at RR Significant effect on survival?	KPS at RR Significant effect on survival?
1	Alhalabi et al. [28], 2024	2017–2022	R	180	NA	NA	NA	NA	48 (27)	34	NA	NA	11.13	NA	NA	NA	yes	no
2	Amini et al. [29], 2015	2007–2014	R	60	57.5	35:25	35	100	9 (15)	NA	NA	-	NA	-	no	I	NA	yes
3	Ammirati et al. [30], 1987	1972–1983	R	35	NA	NA	NA	0	35 (100)	NA	19.1	-	NA	-	yes	NA	yes	yes
4	Archavlis et al. [31], 2013	2005–2010	R	111	55.8	62:49	81	0	36 (32.4)	NA	16	12	NA		yes	yes	NA	yes
5	Archavlis et al. [32], 2014	2008–2011	P	66	58.1	34:32	NA	66	20 (22.2)	NA	20.5	14	8	5	NA	yes	NA	NA
6	Azizi et al. [33], 2001	1998–2000	R	109	54	64:45	NA	0	33 (100)	NA	18.3	12.7	NA		NA	I	NA	yes
7	Azoulay et al. [34], 2017	2005–2012	R	180	58	109:71	NA	0	69 (38.3)	NA	NA		-	6.56	yes	I	NA	yes
8	Barker et al. [35], 1998	1988–1993	R	223	54	140:83	26	0	46 (17.2)	8	17	NA	9	NA	yes	I	NA	yes
9	Bekar et al. [36], 2012	2001–2010	R	161	54.8	88:73	101	100	50 (31.1)	27	26.7	12.2	NA		yes	yes	NA	yes
10	Bloch et al. [37], 2012	2005–2009	R	107	53.7	51:56	52	100	107 (100)	57	19	-	10	-	yes	NA	yes	yes
11	Boiardi et al. [38], 1999	1991–1993	P	54	55	NA	NA	0	15 (27.7)	NA	27.6	16.3	NA		NA	yes	NA	NA
12	Boiardi et al. [39], 2008	2004–2006	R	276	57	165:111	NA	0	115 (41.6)	NA	NA		8	5	NA	yes	yes	NA
13	Brandes et al. [40], 2016	2005–2014	R	270	50.7	178:92	NA	100	270 (100)	128	27.6	-	11.4	-	yes	NA	yes	no
14	Brem et al. [41], 1995	NR	P	145	NA	NA	NA	NA	145 (100)	NA	NA		NA		NA	NA	yes	yes
15	Carson et al. [42], 2007	1995–2002	P	219	NA	NA	NA	NA	219 (100)	NA	-		-		NA	no	NA	yes
16	Chaichana et al. [43], 2013	1997–2007	R	578	55	347:231	102	100	224 (38.8)	35	15.5	6.8	NA		yes	yes	NA	yes
17	Chen et al. [44], 2016	2004–2014	R	65	56.2	43:22	29	100	20 (30.8)	10	25.4	11.6	13.5	5.8	no	yes	no	no
18	Clark et al. [45], 2012	2005–2009	R	174	54	104:70	46	100	174 (100)	NA	22.5	-	NA	-	NA	yes	NA	NA
19	Clarke et al. [46], 2011	1998–2008	P	593	NA	NA	NA	69	181 (30.5)	NA	-		7.8	6.9	NA	no	NA	no
20	Coburger et al. [47], 2017	2008–2014	R	170	60	107:63	164	100	46 (27.1)	NA	31	-	NA		yes	yes	NA	yes
21	Daneyemez et al. [48], 1998	1985–1995	R	72	NA	NA	32	0	14 (20.6)	NA	17	NA	NA	NA	yes	NA	NA	yes
22	Darakchiev et al. [49], 2008	1998–2002	P	34	53	25:09	NA	NA	34 (100)	29	-		17.2	-	NA	yes	yes	yes
23	De Bonis et al. [18], 2013	2002–2008	R	76	59	43:33	76	100	33 (43.4)	11	NA		14	8	no	yes	no	yes
24	De Cock et al. [50], 2014	2008–2011	R	207	NA	NA	NA	100	16 (8)	NA	29.7	18.9	NA		NA	I	NA	NA
25	Delgado-Ferndandez et al. [51], 2017	2010–2015	R	121	62.2	71:50	59	100	31 (25.6)	NA	24.2	8.4	NA		yes	yes	NA	yes
26	Dirks et al. [52], 1993	NR	R	43	53	27:16	NA	NA	43 (100)	NA	14.2	-	4.8	-	NA	yes	NA	NA
27	Durmaz et al. [53], 1997	1985–1995	R	46	47	24:22	27	NA	16 (34.8)	NA	13.25		17.8	9.5	yes	yes	NA	yes
28	Ening et al. [54], 2015	2006–2011	R	141	60.6	76:65	32	100	53 (37.6)	NA	19	13	NA		NA	yes	NA	yes
29	Filippini et al. [55], 2008	1997–2003	R	676	58	418:258	50	NA	173 (25.6)	NA	13.6		6.1		yes	no	NA	NA
30	Franceschi et al. [56], 2015	2005–2010	R	232	52	NA	NA	100	102 (44)	NA	25.8	18.6	9.6	7.5	NA	no	NA	yes
31	Gately et al. [57], 2017	2006–2015	R	776	63	456:320	519	100	51 (6.6)	NA	11		14.27	9.37	yes	I	NA	NA
32	Goldman et al. [58], 2018	2005–2014	R	163	62	111:52	NA	53	89 (54.6)	NA	20	18	9	NA	yes	no	yes	yes
33	González et al. [59], 2022	2005–2019	R	350	NA	NA	214	100	33	NA	25	17	NA	NA	yes	yes	NA	yes
34	Gorlia et al.[60], 2012	1999–2010	P	300	53.5	196:104	93	46	37 (12.3)	NA	NA		6.2		NA	no	NA	yes
35	Guyotat et al. [61], 2000	NR	R	54	NA	NA	NA	100	18 (33)	NA	NA		5	2	NA	yes	NA	no
36	Hager et al. [62], 2018	NR	R	59	71	NA	NA	100	27 (45.8)	11	22.64	NA	NA		NA	yes	NA	NA
37	Harsh et al. [63], 1987	1975–1984	R	39	45.5	22:17	NA	NA	39 (100)	NA	20.5	-	9	-	NA	NA	NA	no
38	Hau et al. [64], 2003	1997–2001	R	168	55	103:65	65	NA	47 (52.2)	NA	15.4	6.5	8.2	2.3	no	yes	NA	yes
39	Helseth et al. [65], 2010	2003–2008	R	516	63.7	304:212	NA	100	65 (12.6)	NA	18.4	8.6	9.9		yes	yes	NA	yes
40	Hickmann et al. [66], 2015	2010–2014	R	69	NA	NA	NA	NA	69 (100)	NA	-		-		NA	yes	yes	NA
41	Honeyman et al. [67], 2024	2014–2022	R	432	NA	281:151	68	43	103 (25.6)	41	22.9		13.7 NA		yes	yes	yes	NA

Table 4 (continued)

No.	Authors, Year	Study Period	Prospective or retrospective	Patients (*n*°)	Age (years; mean)	M: F	MCER at 1 st Surgery (*n*°)	Patients receiving STUPP (%)	Patients with RR, *n*° (%)	MCER at 2nd Surgery (*n*°)	RR Cohort OS from IS	Non-RR Cohort OS from IS	RR Cohort OS from RR	Non-RR Cohort OS from RR	EOR at 1 st Surgery Significant effect on Survival?	RR Significant effect on survival?	EOR at RR Significant effect on survival?	KPS at RR Significant effect on survival?
42	Hong et al. [55, 55, 68, 68], 2013	2006–2010	R	42	57.5	19:23	34	100	42 (100)	28	19	-	NA		yes	yes	no	yes
43	Kamp et al. [69], 2015	2009–2013	R	13	59.5	10:03	NA	92	13 (100)	NA	-		11	-	NA	yes	NA	NA
44	Keles et al. [70], 1999	1980–1991	R	92	51	51:41	15	NA	52 (49)	6	15.25		NA		yes	yes	yes	yes
45	Kim et al. [71], 2015	2002–2011	R	222	NA	NA	83	100	38 (17.1)	NA	18.7		13.2	15.5	no	no	NA	yes
46	Landy et al. [72], 1994	1986–1992	R	12	NA	NA	NA	0	12 (100)	NA	NA	-	8	-	NA	I	NA	yes
47	Linde et al. [73], 2017	2005–2014	R	299	56	202:97	74	66	56 (18.7)	23	NA		-	7.3	no	yes	NA	no
48	Ma et al. [74], 2009	1999–2004	R	205	NA	141:64	131	2	52 (25.3)	NA	16	10.7	NA		yes	no	yes	NA
49	Mandl et al. [75], 2008	1999–2005	R	91	NA	NA	NA	NA	20 (22)	NA	15.5		8.5	7	NA	NA	NA	yes
50	McGirt et al. [76], 2009	1996–2007	R	949	51	564:385	333	100	294 (31)	NA	13	NA	11	NA	yes	yes	yes	yes
51	McNamara et al. [77], 2014	2004–2011	R	584	59	363:221	NA	100	107 (18.3)	0	20.9	9.9	7		yes	yes	no	yes
52	Michaelsen et al. [78], 2013	2005–2010	P	225	59.2	145:80	89	100	74 (32.8)	NA	14.3		6.3		NA	yes	no	NA
53	Mühling et al. [79], 1999	1990–1996	R	35	48	20:15	21	NA	35 (100)	24	NA	-	6.7	-	yes	NA	yes	NA
54	Mut et a. [80], 2025	2014–2025	R	60	NA	36:24	16	95	30 (50)	8	23.87	9.17	11.35	2	no	yes	I	yes
55	Nabavi et al. [81], 2009	2003–2005	P	21	NA	NA	NA	NA	21 (100)	NA	-		7.4	-	NA	yes	NA	NA
56	Nava et al. [82], 2014	2004–2012	P	303	NA	206:97	NA	60	98 (35)	NA	NA		8.9		NA	no	NA	yes
57	Oppenlander et al. [83], 2014	2001–2011	R	170	55.2	105:65	NA	100	170 (100)	110	19	-	5.2	-	yes	NA	yes	yes
58	Ortega et al. [82, 84], 2016	2003–2012	R	202	58	121:81	124	100	119 (59)	NA	25.5	21.1	NA		yes	I	yes	yes
59	Osawa et al. [85], 2025	2010–2023	R	41	NA	24:17	13	88	41 (100)	20	NA		NA 18.7	NA	NA	NA	yes	NA
60	Parakh et al. [86], 2016	2006–2008	R	194	61.7	129:65	NA	56	95 (49)	NA	14	10	NA		NA	no	NA	NA
61	Park et al. [87], 2010	NA	R	34	50.5	22:12	NA	NA	34 (100)	NA	NA	-	7.4	-	NA	NA	NA	yes
62	Park et al. [88], 2013	2000–2010	R	55	50	33:22	NA	NA	55 (100)	37	13	-	10	-	NA	NA	no	yes
63	Perrini et al. [89], 2016	2001–2015	R	48	59.2	29:19	27	100	48 (100)	20	21	-	7	-	yes	NA	yes	no
64	Pinsker et al. [90], 2002	1993–1998	R	38	54	25:13	26	0	38 (100)	21	14.2	-	5.7	-	yes	yes	yes	yes
65	Quick et al. [91], 2014	2007–2010	R	40	58	18:22	23	100	40 (100)	29	21.7	-	13.5	-	yes	NA	yes	yes
66	Ringel et al. [92], 2016	2006–2010	R	503	58	313:190	238	93	503 (100)	237	25	-	11.9	-	yes	yes	yes	yes
67	Rostomily et al. [93], 1994	1986–1990	P	31	NA	21:10	NA	NA	22 (71)	NA	NA		8.2		NA	I	NA	NA
68	Rusthoven et al. [94], 2011	2001–2009	R	34	NA	NA	NA	62	34 (100)	NA	22.2	14.2	9.3	4.9	no	NA	NA	NA
69	Salcman et al. [95], 1982	1978–1981	P	57	NA	NA	NA	0	32 (56.1)	NA	16.2		NA		NA	yes	NA	no
70	Sastry et al. [96], 2018	2008–2015	R	368	60	NA	118	96	77 (20.9)	26	19.5		12.8	7	no	yes	no	yes
71	Scorsetti et al. [97], 2015	2006–2014	R	43	51	22:21	24	100	21 (48.8)	NA	17	6	11		no	yes	NA	no
72	Shrieve et al. [98], 1999	1988–1995	P	78	51	45:33	7	NA	39 (50)	NA	24.2	18.2	12.4	-	no	yes	NA	NA
73	Skeie et al. [99], 2012	1996–2007	R	77	55.3	49:28	77	48	45 (58.4)	NA	21	18	15	9	NA	yes	NA	no
74	Stark et al. [100], 2007	1990–2002	R	345	62	190:155	206	0	107 (31)	NA	15		12		yes	yes	NA	NA
75	Subach et al. [101], 1999	1996–1998	R	45	54	31:14	NA	NA	45 (100)	NA	24.2	-	12.5	-	NA	NA	NA	NA
76	Suchorska et al. [19], 2016	2009–2013	P	105	57	69:36	NA	100	71 (68)	40	NA		11.4	9.8	NA	I	yes	NA
77	Sughrue et al. [102], 2015	1995–2009	R	104	NA	NA	0	100	104 (100)	21	NA	-	NA	-	yes	no	NA	yes
78	Terasaki et al. [103], 2007	2002–2005	P	35	NA	NA	4	0	7 (20)	5	15.1		9		no	yes	no	NA
79	Tugcu et al. [104], 2010	1998–2004	R	50	54.1	28:22	28	NA	11 (22)	NA	9.6	6.7	6.9		yes	yes	NA	yes
80	Tully et al. [105], 2016	2010–2013	R	204	66	125:79	60	70	49 (24)	NA	20.1	9	7.6		no	yes	NA	no
81	Voisin et al. [106], 2022	2011–2021	R	174	NA	NA	NA	NA	87 (50)	NA	NA	NA	NA		NA	yes	NA	NA
82	Wann et al. [107], 2018	2009–2015	R	120	56	65:55	26	100	60 (50)	NA	22	14	9.6	4.7	yes	yes	NA	yes
83	Woernle et al. [108], 2015	2007–2011	R	98	55	64:34	69	85	40 (40.8)	27	18.9	14.8	NA		no	I	NA	no

Table 4 (continued)

No.	Authors, Year	Study Period	Prospective or retrospective	Patients (n^o)	Age (years; mean)	M: F	MCER at 1 st Surgery (n^o)	Patients receiving STUPP (%)	Patients with RR, n^o (%)	MCER at 2nd Surgery (n^o)	RR Cohort OS from IS	Non-RR Cohort OS from IS	RR Cohort OS from RR	Non-RR Cohort OS from RR	EOR at 1 st Surgery Significant effect on Survival?	RR Significant effect on survival?	EOR at RR Significant effect on survival?	KPS at RR Significant effect on survival?
84	Woodworth et al. [109], 2013	1996–2009	R	59	53	21:38	27	NA	21 (35.6)	NA	20		8		yes	NA	no	yes
85	Woo et al. [110], 2024	2006–2019	R	1032	NA	NA	NA	NA	190 (18)	NA	NA		NA 16.9	9.8	NA	yes	yes	NA
86	Yong et al. [111], 2014	2002–2012	R	97	49	28:69	NA	100	97 (100)	38	NA	-	12.4	-	yes	NA	no	yes
87	Zanello et al. [112], 2017	2005–2015	R	777	58	504:273	458	46	179 (23)	NA	19		8		yes	yes	NA	yes

I, non-significant increase; IS, initial surgery; RR, repeat resection; maximal contrast-enhancing (CE) resection (MCER); EOR, extent of resection; OS, overall survival; KPS, Karnofsky performance status; NA, not available; P, prospective; R, retrospective; NA, not available

merely a reflection of favorable baseline patient characteristics. Consistently, studies adopting volumetric-based surgical criteria have demonstrated improved outcomes following near-complete resection [20, 92, 93]. 5-aminolevulinic-acid (5-ALA) guided surgery may facilitate MCER, particularly by enhancing the visualization of tumor margins in the recurrent setting. As reported by Hickman et al. [66], analyzing patients with recurrent high-grade gliomas reoperated with or without the aid of intraoperative 5-ALA, reported that EOR > 98% at second surgery significantly improve OS in IV grade gliomas ($p = 0.019$) and in cases with fluorescent tumors surgeons achieved MCER more often.

The role of neoadjuvant and adjuvant therapies at recurrence remains controversial, and standardized treatment protocols are lacking. While selected randomized trials have reported prolonged disease-free survival with salvage systemic or immunotherapeutic approaches administered before surgery or radiotherapy, our multicenter analysis did not identify an association between perioperative oncological treatments and post-recurrence survival, suggesting that their impact may be highly context-dependent and influenced by patient selection and treatment sequencing [18, 114–116].

Clinical outcome and functional risk

Neurological morbidity after reoperation for rGBM remains insufficiently reported, as most studies primarily focus on survival outcomes with limited integration of quality-of-life measures. Our findings suggest that the EOR at second surgery may be associated with PO, considered as good functional status at 3 months and survival longer than six months. Indeed, RANO rClass 1 resection was significantly correlated with a KPS≥70 at 90 days and with PRS≥6 months. However, given the retrospective design, these associations should be interpreted cautiously, as selection and survivorship biases cannot be excluded.

Second surgery may improve survival, according to current research, although outcome assessments frequently fail to account for postoperative functional outcomes [106, 110, 117]. A large multicenter retrospective study Ringel et al. [92] reported a modest but measurable increase in both neurologic and non-neurologic complications after reoperation for rGBM compared with initial surgery, with higher rates of non-neurologic events, transient neurological deficits, and permanent neurological deficits. This emphasizes the significance of a customized evaluation of functional risk and benefit, especially considering the varying impact of resection extent on postoperative deficits among rGBM subgroups [118, 119]. In order to support patient-centered surgical decision-making and highlight the requirement for prospective comparative studies across surgical and

Table 5 Summary of Robvis (Risk-Of-Bias VISualization)

No.	Authors, Year	Study design	Selection bias	Performance bias	Detection bias	Attrition Bias	Overall risk of Bias
1	Alhalabi et al. [28], 2024	retrospective	Serious	Serious	Moderate	Serious	Serious
2	Amini et al. [29], 2015	retrospective	Low	Low	Low	Moderate	Low
3	Ammirati et al. [30], 1987	retrospective	Serious	Low	Low	Serious	Moderate
4	Archavlis et al. [31], 2013	retrospective	Low	Low	Low	Low	Low
5	Archavlis et al. [32], 2014	prospective	Low	Serious	Moderate	Low	Moderate
6	Azizi et al. [33], 2001	retrospective	Low	Serious	Moderate	Moderate	Moderate
7	Azoulay et al. [34], 2017	retrospective	Low	Serious	Low	Moderate	Moderate
8	Barker et al. [35], 1998	retrospective	Low	Moderate	Low	Moderate	Moderate
9	Bekar et al. [36], 2012	retrospective	Low	Low	Low	Low	Low
10	Bloch et al. [37], 2012	retrospective	Low	Low	Low	Serious	Moderate
11	Boiardi et al. [38], 1999	prospective	Moderate	Low	Moderate	Low	Moderate
12	Boiardi et al. [39], 2008	retrospective	Low	Low	Moderate	Low	Low
13	Brandes et al. [40], 2016	retrospective	Low	Low	Low	Serious	Moderate
14	Brem et al. [41], 1995	prospective	Serious	Serious	Moderate	Serious	Moderate
15	Carson et al. [42], 2007	prospective	Serious	Serious	Moderate	Moderate	Moderate
16	Chaichana et al. [43], 2013	retrospective	Low	Low	Low	Low	Low
17	Chen et al. [44], 2016	retrospective	Low	Low	Low	Low	Low
18	Clark et al. [45], 2012	retrospective	Low	Low	Moderate	Low	Low
19	Clarke et al. [46], 2011	prospective	Serious	Moderate	Moderate	Moderate	Moderate
20	Coburger et al. [47], 2017	retrospective	Low	Low	Low	Low	Low
21	Daneyemez et al. [48], 1998	retrospective	Serious	Low	Low	Serious	Moderate
22	Darakchiev et al. [49], 2008	prospective	Low	Serious	Moderate	Low	Moderate
23	De Bonis et al. [18], 2013	retrospective	Low	Low	Low	Low	Low
24	De Cock et al. [50], 2014	retrospective	Serious	Moderate	Moderate	Moderate	Moderate
25	Delgado-Ferndandez et al. [51], 2017	retrospective	Low	Low	Low	Low	Low
26	Dirks et al. [52], 1993	retrospective	Low	Serious	Moderate	Low	Moderate
27	Durmaz et al. [53], 1997	retrospective	Low	Moderate	Low	Low	Moderate
28	Ening et al. [54], 2015	retrospective	Low	Low	Moderate	Low	Low
29	Filippini et al. [55], 2008	retrospective	Low	Moderate	Low	Moderate	Moderate
30	Franceschi et al. [56], 2015	retrospective	Moderate	Moderate	Moderate	Moderate	Moderate
31	Gately et al. [57], 2017	retrospective	Low	Low	Low	Moderate	Moderate
32	Goldman et al. [58], 2018	retrospective	Low	Moderate	Low	Moderate	Moderate
33	González et al. [59], 2022	retrospective	Serious	Low	Low	Low	Low
34	Gorlia et al.[60], 2012	prospective	Low	Low	Moderate	Moderate	Moderate
35	Guyotat et al. [61], 2000	retrospective	Serious	Moderate	Moderate	Low	Moderate
36	Hager et al. [62], 2018	retrospective	Moderate	Moderate	Moderate	Low	Moderate
37	Harsh et al. [63], 1987	retrospective	Low	Serious	Moderate	Serious	Moderate
38	Hau et al. [64], 2003	retrospective	Low	Moderate	Low	Low	Moderate
39	Helseth et al. [65], 2010	retrospective	Low	Moderate	Low	Low	Moderate
40	Hickmann et al. [66], 2015	retrospective	Serious	Serious	Moderate	Low	Moderate
41	Honeyman et al. [67], 2024	retrospective	Moderate	Low	Low	Low	Moderate
42	Hong et al. [55, 68], 2013	retrospective	Low	Low	Low	Low	Low
43	Kamp et al. [69], 2015	retrospective	Low	Moderate	Moderate	Low	Moderate
44	Keles et al. [70], 1999	retrospective	Low	Moderate	Low	Low	Moderate
45	Kim et al. [71], 2015	retrospective	Serious	Low	Low	Moderate	Moderate
46	Landy et al. [72], 1994	retrospective	Serious	Low	Moderate	Moderate	Moderate
47	Linde et al. [73], 2017	retrospective	Low	Low	Low	Low	Low
48	Ma et al. [74], 2009	retrospective	Moderate	Low	Low	Moderate	Moderate
49	Mandl et al. [75], 2008	retrospective	Serious	Serious	Moderate	Serious	Moderate
50	McGirt et al. [76], 2009	retrospective	Low	Low	Low	Low	Low
51	McNamara et al. [77], 2014	retrospective	Low	Low	Low	Low	Low
52	Michaelsen et al. [78], 2013	prospective	Low	Low	Moderate	Low	Moderate
53	Mühling et al. [79], 1999	retrospective	Low	Moderate	Low	Serious	Moderate
54	Mut et a. [80], 2025	retrospective	Moderate	Low	Low	Low	Moderate

Table 5 (continued)

No.	Authors, Year	Study design	Selection bias	Performance bias	Detection bias	Attrition Bias	Overall risk of Bias
55	Nabavi et al. [81], 2009	prospective	Serious	Serious	Moderate	Low	Moderate
56	Nava et al. [82], 2014	prospective	Moderate	Moderate	Moderate	Moderate	Moderate
57	Oppenlander et al. [83], 2014	retrospective	Low	Low	Low	Serious	Moderate
58	Ortega et al. [82, 84], 2016	retrospective	Low	Low	Low	Moderate	Moderate
59	Osawa et al. [85], 2025	retrospective	Moderate	Low	Moderate	Serious	Moderate
60	Parakh et al. [86], 2016	retrospective	Low	Moderate	Moderate	Moderate	Moderate
61	Park et al. [87], 2010	retrospective	Low	Serious	Moderate	Serious	Moderate
62	Park et al. [88], 2013	retrospective	Low	Serious	Moderate	Serious	Moderate
63	Perrini et al. [89], 2016	retrospective	Low	Low	Low	Serious	Moderate
64	Pinsker et al. [90], 2002	retrospective	Low	Low	Low	Low	Low
65	Quick et al. [91], 2014	retrospective	Low	Low	Low	Serious	Moderate
66	Ringel et al. [92], 2016	retrospective	Low	Moderate	Low	Low	Moderate
67	Rostomily et al. [93], 1994	prospective	Moderate	Serious	Moderate	Moderate	Moderate
68	Rusthoven et al. [94], 2011	retrospective	Serious	Moderate	Low	Serious	Moderate
69	Salcman et al. [95], 1982	prospective	Serious	Moderate	Moderate	Low	Moderate
70	Sastry et al. [96], 2018	retrospective	Moderate	Moderate	Low	Low	Moderate
71	Scorsetti et al. [97], 2015	retrospective	Low	Low	Low	Low	Low
72	Shrieve et al. [98], 1999	prospective	Low	Moderate	Low	Low	Moderate
73	Skeie et al. [99], 2012	retrospective	Low	Moderate	Moderate	Low	Moderate
74	Stark et al. [100], 2007	retrospective	Low	Low	Low	Low	Low
75	Subach et al. [101], 1999	retrospective	Low	Serious	Moderate	Serious	Moderate
76	Suchorska et al. [19], 2016	prospective	Low	Moderate	Moderate	Moderate	Moderate
77	Sughrue et al. [102], 2015	retrospective	Serious	Low	Low	Moderate	Moderate
78	Terasaki et al. [103], 2007	prospective	Serious	Low	Low	Low	Moderate
79	Tugcu et al. [104], 2010	retrospective	Low	Moderate	Low	Low	Moderate
80	Tully et al. [105], 2016	retrospective	Low	Moderate	Low	Low	Moderate
81	Voisin et al. [106], 2022	retrospective	Serious	Serious	Moderate	Low	Moderate
82	Wann et al. [107], 2018	retrospective	Low	Low	Low	Low	Low
83	Woernle et al. [108], 2015	retrospective	Low	Moderate	Low	Moderate	Moderate
84	Woodworth et al. [109], 2013	retrospective	Low	Moderate	Low	Serious	Moderate
85	Woo et al. [110], 2024	retrospective	Serious	Serious	Moderate	Low	Moderate
86	Yong et al. [111], 2014	retrospective	Low	Low	Low	Serious	Moderate
87	Zanello et al. [112], 2017	retrospective	Low	Moderate	Low	Low	Moderate

non-surgical treatment strategies, this nationwide multicenter study integrates KPS and PRS for rGBM.

Positive outcome: beyond survival

While PRS remains the most commonly reported endpoint in studies on rGBM, survival alone may not fully capture the clinical value of reoperation [76, 118, 119]. Beyond survival metrics alone, the present study emphasizes the importance of integrating functional outcomes into survival benefit. In this context, we introduced the concept of PO, defined as the combination of PRS ≥ 6 months and preservation of functional independence (KPS ≥ 70 at 90 days after reoperation). This composite endpoint was designed to better reflect real-world clinical decision-making, where prolonging survival without unacceptable functional deterioration represents the primary therapeutic goal [43, 76]. PO addresses a significant drawback of survival-only objectives in recurrent glioblastoma, where intensive treatments may increase morbidity without equivalent gains in quality of life, by separating patients who have a significant clinical benefit from those who merely live longer [118, 119]. PO is a practical, patient-centered objective from a methodological perspective that could enhance outcome evaluation and patient selection in upcoming surgical and observational research [20].

Propensity score matching (PSM): robustness of surgical effect

Propensity score matching was used to evaluate the strength of the relationship between surgical extent and post-recurrence survival due to the non-randomized selection of patients for reoperation at recurrence. Higher preoperative

functional level and other positive baseline features, which are proven predictors of survival, may be present in patients receiving RANO rClass I resection. Propensity score matching made it possible to estimate the independent influence of surgical extent on outcome more accurately by balancing these important factors across rClass groups.

Importantly, the persistence of a significant survival benefit after matching indicates that the advantage associated with RANO rClass I resection is not solely attributable to selection bias, but reflects a clinically meaningful effect of maximal cytoreduction, in line with prior volumetric and RANO-resect–based analyses. These results support supramaximal contrast-enhancing excision as a treatment objective in carefully selected patients with recurrent glioblastoma where functional preservation can be reliably achieved, even though residual confounding inherent to retrospective research cannot be completely avoided [20, 22, 76, 92].

Biological and molecular modifiers of outcome

Beyond clinical and surgical factors, biological and molecular tumor features may drive the prognosis after reoperation in rGBM. In our cohort, radiological features reflecting tumor biology—including the absence of ependymal or subventricular zone involvement and lower tumor volume at recurrence—were associated with longer post-recurrence survival, consistent with less infiltrative disease and greater surgical amenability [87, 88].

In this investigation, MGMT promoter methylation was associated with improved PRS when present at first (p = 0.024) and second surgery (p = 0.030), although its prognostic and predictive value in rGBM remains debated. Brandes et al. reported that MGMT methylation at diagnosis retains prognostic significance, whereas MGMT status at recurrence does not independently predict survival after second surgery [40, 41, 120]. Conversely, Franceschi et al. observed a significant association between MGMT methylation at diagnosis and both overall and progression-free survival [56], and several studies have suggested that molecular reassessment at recurrence, including MGMT and IDH status, may provide additional prognostic information [121–124].

Consistent with this latter observation, Chai et al. demonstrated a strong association between MGMT promoter methylation and prolonged survival in IDH-mutant glioblastoma at both first and second surgery (p = 0.0001) [121]. Similarly, Montemurro et al. reported that MGMT methylation influenced overall survival in univariate analyses at first (p = 0.038) and second surgery (p = 0.107), while p53 mutation status appeared to affect survival predominantly at recurrence (p = 0.01) [122]. In addition, Lam et al. [125] suggested that MGMT methylation may be prognostic for both OS and progression free survival. In our multivariate analysis, patients with unmethylated MGMT appeared to have a higher risk of death and recurrence, corroborating evidence from prior studies.

IDH mutation has been consistently associated with longer survival in GMB, demonstrating its prognostic significance, especially in the recurrent situation [126–128]. In our cohort, IDH mutation at first surgery was more frequently observed in patients with better overall survival, higher postoperative KPS, and PO after reoperation, although no statistically significant associations with study endpoints were detected.

ATRX inexpression, frequently observed in rGBM and often co-occurring with IDH and TP53 mutations, has likewise been reported as a favorable prognostic marker [129–131] and was associated with KPS ≥ 90 at recurrence in our analysis. Conversely, there is ongoing debate on the prognostic significance of PTEN loss in rGBM [132–134]. In our group, PTEN inexpression at first surgery was linked to better postoperative KPS and PO.

Overall, our results suggest that the outcome following reoperation in rGBM is influenced by the interaction of genetic characteristics with clinical and surgical variables. However, biomarkers as MGMT and IDH provide important prognostic insights but cannot be used alone for survival prediction.

They should instead be integrated with standardized clinical and volumetric factors, while accounting for survivorship bias in recurrent glioblastoma studies [135–137].

Integration with existing evidence and clinical implications

The systematic review, which demonstrates that reoperation may provide a survival benefit in carefully selected patients with rGBM, provides strong support for the multicenter study's findings. Reoperation and preserved functional status at recurrence was linked to better OS in 68% and 78% of studies, respectively, across the literature, highlighting the significance of patient selection [18, 19, 28–112]. Likewise, maximal or supramaximal CE resection at first and second surgery was associated with improved survival in approximately two-thirds of reports.

Notably, by using standardized volumetric criteria in accordance with the RANO-resect paradigm, our results expand on previous findings. Our data show that a significant survival benefit from reoperation is most consistently observed when minimal residual contrast-enhancing tumor can be achieved, which is consistent with recent RANO-resect–based analyses and meta-analyses [20–22]. This supports the use of quantitative volumetric thresholds over subjective surgical definitions.

From a clinical perspective, this investigation underpins a focused and customized strategy to reoperation, which should be taken into consideration within a multidisciplinary framework in patients who have positive radiological

features, low tumor load, and preserved functional status. Overall, the agreement between our multicenter data and current evidence supports reoperation as a therapeutic option in selected rGBM patients and emphasizes the need for patient-centered outcome measures and standardized surgical endpoints in future research.

Limitations and future directions

Several limitations of this study should be acknowledged. First, the retrospective design inherently carries a risk of selection bias, which cannot be completely eliminated despite the use of propensity score matching. Unfortunately, PSM was only possible for patients with complete data, resulting in a highly selected subgroup and limiting generalizability. Prospective or randomized trials are needed to validate and reinforce these findings, even if PSM partially reduced selection bias inherent in the retrospective approach.

Second, the cohort's multicenter design might have contributed to variations in perioperative care, surgical techniques, and adjuvant treatment plans. Lastly, deeper biological stratification was limited because molecular reevaluation at recurrence was not consistently available.

Lastly, existing studies predominantly focused on OS, with less attention to KPS and no prior mention of PO, leading to data abstraction focused solely on shared variables and limiting comparisons. Nonetheless, our study stands as the largest case series to date analyzing OS, KPS, and introducing PO as a novel parameter combining survival and quality of life, thereby offering valuable selective criteria for rGBM reoperation.

Future studies should incorporate randomized or pragmatic trial designs to more effectively address residual confounding and to better delineate the independent role of reoperation within evolving treatment strategies for recurrent glioblastoma.

Conclusions

Surgical indications for rGBM remain debated, although the majority of available studies report a survival benefit in this clinical setting. Careful patient selection is essential to optimize clinical outcomes. Based on the results of this multicenter retrospective analysis, a KPS$\geq$70 and the achievement of a RANO-resect Class 1 resection at second surgery emerge as key factors associated with both survival benefit and functional preservation. Additional parameters, including tumor volume at recurrence, ependymal involvement, and MGMT promoter methylation status, should also be considered when assessing surgical option at the time of tumor recurrence. Reoperation for rGBM should be evaluated in terms of significant clinical benefit, not just survival. By combining survival and functional preservation, the Positive Outcome objective provides a useful, patient-centered framework and encourages its implementation as a supplementary endpoint in subsequent research, especially for those cases who achieve RANO-resect Class 1 resection with preserved functional status. Cross-sectional and randomized cohort studies are thus warranted to establish robust, evidence-based guidelines for the management of rGBM.

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